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* * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:28:07 ON 12 MAY 2006

=> file reg


http://www.cas.org/ONLINE/UG/regprops.html



=> e antitrypsin/cn
E1            1      ANTITRITON, MOL. WITH TRITON (T+2.HIVIN.T2)/CN
E2            1      ANTITROMBOSIN/CN
E3            1 --> ANTITRYPSIN/CN
E4            1      ANTITRYPSIN (HUMAN CLONE MGC:23251 IMAGE:4866432 CLADE A MEM
                     BER 4)/CN
E5            1      ANTITRYPSIN PITTSBURGH/CN
E6            1      ANTITRYPSIN VAGS (HUMAN CLONE 651658_181-35-2-0-C8-F PRECURS
                     OR)/CN
E7            1      ANTITRYPSIN, CRYPAAT (HUMAN CLONE 588098_184-11-4-0-H4-F PRE
                     CURSOR)/CN
E8            1      ANTITUMOR AGENTS, ANTINEOPLASTONS/CN
E9            1      ANTITUMOR ANTIBIOTIC AGPM/CN
E10           1      ANTITUMOR ANTIVIRAL A-77543/CN
E11           1      ANTITUMOR BE 70016/CN
E12           1      ANTITUMOR JL 68/CN

=> s e3-e4
              1 ANTITRYPSIN/CN
              1 "ANTITRYPSIN (HUMAN CLONE MGC:23251 IMAGE:4866432 CLADE A MEMBER
                4)"/CN
L1            2 (ANTITRYPSIN/CN OR "ANTITRYPSIN (HUMAN CLONE MGC:23251 IMAGE:486
                6432 CLADE A MEMBER 4)"/CN)

=> file caplus

http://www.cas.org/infopolicy.html

=> s l1
L2         5988 L1

=> s l1/purif.

=> s l1/prep
           5988 L1
        3466522 PREP/RL
L3          478 L1/PREP
                  (L1 (L) PREP/RL)



=> FIL REGISTRY


http://www.cas.org/ONLINE/UG/regprops.html

=> S 9041-92-3/RN

L5            1 9041-92-3/RN
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=> D L5 RN CCN 1-

Y
L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN     ***9041-92-3***    REGISTRY
CN   Trypsin inhibitor, .alpha.1- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   .alpha.1-Antiprotease;  .alpha.1-Antiproteinase;  .alpha.1-Antitrypsin;
     .alpha.1-Antitrypsin Pittsburgh mutant;  .alpha.1-Antitrypsin Portland;
     .alpha.1-AT;  .alpha.1-Protease inhibitor;  .alpha.1-Proteinase inhibitor;
     .alpha.1-Trypsin inhibitor;  Antitrypsin Pittsburgh;  Aralast;  Prolastin;
     Respitin;  Serpin A 1;  Zemaira


=> SET NOTICE 1 DISPLAY

NOTICE SET TO 1 U.S. DOLLAR FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=> D L5 RN IN 1-


L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN     ***9041-92-3***    REGISTRY
IN   Trypsin inhibitor, .alpha.1- (9CI)



=> SET NOTICE 1 DISPLAY

NOTICE SET TO 1 U.S. DOLLAR FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=> D L5 SQIDE 1-



L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN     ***9041-92-3***    REGISTRY
CN   Trypsin inhibitor, .alpha.1- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   .alpha.1-Antiprotease
CN   .alpha.1-Antiproteinase
CN   .alpha.1-Antitrypsin
CN   .alpha.1-Antitrypsin Pittsburgh mutant
CN   .alpha.1-Antitrypsin Portland
CN   .alpha.1-AT
CN   .alpha.1-Protease inhibitor
CN   .alpha.1-Proteinase inhibitor
CN   .alpha.1-Trypsin inhibitor
CN   Antitrypsin Pittsburgh
CN   Aralast
CN   Prolastin
CN   Respitin
CN   Serpin A 1
CN   Zemaira
DR   9082-50-2, 124542-00-3
MF   Unspecified
CI   COM, MAN
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO,
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CA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5823 REFERENCES IN FILE CA (1907 TO DATE)
317 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5833 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.27	22.88

STN INTERNATIONAL LOGOFF AT 13:33:37 ON 12 MAY 2006

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3556	alpha ADJ2 "1" ADJ2 antitrypsin	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:43
L2	76	aralast or prolastin or respitin or zemaira	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:44
L3	3606	l1 or l2	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:44
L4	115	fibromyalgia and l3	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:44
L5	13	fibromyalgia same l3	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:48
L6	107	l4 NOT timmer.in.	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:48
L7	88	l6 and @pd<"20050919"	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:58
L8	402	blanco.in.	US-PGPUB; USPAT	ADJ	ON	2006/05/12 13:58
L9	4	blanco.in. and ignacio	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:14
L10	2066	l3 and $inflammatory	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:16
L11	430	l3 same $inflammatory	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:16
L12	420	l11 not l6	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:16
L16	48	l15 same anti-inflammatory	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:18
L17	38	l16 and @pd<"20050919"	US-PGPUB; USPAT	ADJ	ON	2006/05/12 14:18

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:44:03 ON 12 MAY 2006

=> file bioscience


=> set plurals on
SET COMMAND COMPLETED

=> index bioscience patents


=> d his

     (FILE 'HOME' ENTERED AT 16:44:03 ON 12 MAY 2006)

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB,
     CIN, CONFSCI, CROPB, CROPU, DDFB, DGENE, DISSABS, DRUGB, DRUGMONOG2,
     DRUGU, EMBAL, EMBASE, ESBIOBASE, FOMAD, ...' ENTERED AT 16:44:11 ON 12
     MAY 2006
               SET PLURALS ON

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 16:44:26 ON 12 MAY 2006
               SEA ALPHA-1 ANTITRYPSIN OR ALPHA-1-ANTITRYPSIN OR ARALAST OR PR
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              77   FILE ADISCTI
              21   FILE ADISINSIGHT
              25   FILE ADISNEWS
              65   FILE AGRICOLA
             103   FILE ANABSTR
               1   FILE ANTE
               4   FILE AQUASCI
             157   FILE BIOENG
            7165   FILE BIOSIS
             553   FILE BIOTECHABS
             553   FILE BIOTECHDS
            1960   FILE BIOTECHNO
             413   FILE CABA
            5752   FILE CAPLUS
              74   FILE CEABA-VTB
             105   FILE CIN
             140   FILE CONFSCI
              93   FILE DDFB
             439   FILE DDFU
            3173   FILE DGENE
             121   FILE DISSABS
              93   FILE DRUGB
               6   FILE DRUGMONOG2
             585   FILE DRUGU
              40   FILE EMBAL
            9306   FILE EMBASE
             750   FILE ESBIOBASE
              12   FILE FROSTI
               9   FILE FSTA
            2481   FILE GENBANK
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              11   FILE HEALSAFE
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              46   FILE IMSDRUGNEWS
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               8   FILE IMSRESEARCH
             737   FILE JICST-EPLUS
               1   FILE KOSMET
             744   FILE LIFESCI
           10208   FILE MEDLINE
              45   FILE NTIS
             611   FILE PASCAL
              32   FILE PHAR
              32   FILE PHARMAML
             210   FILE PHIN
             436   FILE PROMT
               1   FILE PROUSDDR
            6279   FILE SCISEARCH
            3063   FILE TOXCENTER
            4077   FILE USPATFULL
             305   FILE USPAT2
               3   FILE VETU
             502   FILE WPIDS
               3   FILE WPIFV
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              11   FILE CAOLD
              53   FILE DPCI
             804   FILE EPFULL
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               3   FILE FRFULL
               8   FILE GBFULL
              17   FILE IMSPATENTS
             211   FILE INPADOC
              16   FILE JAPIO
               4   FILE KOREAPAT
               1   FILE PATDD
              45   FILE PATDPA
             371   FILE PATDPAFULL
             858   FILE PCTFULL
               6   FILE RUSSIAPAT
L1              QUE ALPHA-1 ANTITRYPSIN OR ALPHA-1-ANTITRYPSIN OR ARALAST OR PR
                ---------

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS, TOXCENTER, GENBANK,
     BIOTECHNO' ENTERED AT 16:50:29 ON 12 MAY 2006
L2         46214 S L1
L3             9 S L2 (P) FIBROMYALGIA
L4         13116 S L2 (P) (PLASMA OR SERUM)
L5           898 S L4 (S) ADMINIST?
L6           397 S L2 (S) ADMINIST?
L7           179 S L6 AND L4
L8            74 DUP REM L7 (105 DUPLICATES REMOVED)
L9            74 S L8 NOT GENBANK
L10         1527 S L2 (P) ADMINIST?
L11          663 S L10 AND L4
L12          216 S L11 (P) DEFICIEN?
L13           93 DUP REM L12 (123 DUPLICATES REMOVED)
L14            0 S L2 (P) INTRAVEOUS
L15          484 S L2 (P) INTRAVENOUS
L16         1719 S L15 OR L10
L17          777 S L16 AND L4
L18          250 S L17 (P) DEFICIEN?
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=> dup rem l18
DUPLICATE IS NOT AVAILABLE IN 'GENBANK'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L18
L19          103 DUP REM L18 (147 DUPLICATES REMOVED)

=> s l19 and py<2006
   1 FILES SEARCHED...
   5 FILES SEARCHED...
L20         102 L19 AND PY<2006

L22           0 L20 AND MG/KG

=> s l20 and level
L23          64 L20 AND LEVEL

=> s l23 and py<2005
   1 FILES SEARCHED...
   5 FILES SEARCHED...
L24          60 L23 AND PY<2005

=> d bib abs 1-25

L24  ANSWER 1 OF 60     MEDLINE on STN
AN   2004478199     MEDLINE
DN   PubMed ID: 15446311
TI   Donor-derived, liver-specific protein expression after bone marrow
     transplantation.
AU   Jenkins D Denison; Streetz Konrad; Tataria Monika; Sahar David; Kurobe
     Masashi; Longaker Michael T; Kay Mark A; Sylvester Karl G
CS   Department of Surgery, Stanford University School of Medicine, Stanford,
     California 94305-5733, USA.
NC   AI41320 (NIAID)
SO   Transplantation,   ***(2004 Aug 27)***   Vol. 78, No. 4, pp. 530-6.
     Journal code: 0132144. ISSN: 0041-1337.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200410
ED   Entered STN: 28 Sep 2004
     Last Updated on STN: 8 Oct 2004
     Entered Medline: 7 Oct 2004
AB   BACKGROUND: Bone marrow transplantation (BMT) may represent a novel
     mechanism to deliver a functional gene to a   ***deficient***   liver.
     Bone marrow-derived hepatocytes are rare and without a defined
     contribution to liver function.  Consequently, the clinical significance
     of BMT to treat liver disease is unclear.  We sought to quantify bone
     marrow-derived hepatocyte protein expression after BMT and determine
     whether the process is inducible with liver injury.  METHODS: Mice
     transgenic for human   ***alpha***  -  ***1***     ***antitrypsin***
     (hAAT) under a hepatocyte-specific promoter were used as bone marrow
     donors.  Adenoviral transduction of modified urokinase plasminogen
     activator (Ad-muPA) was used to induce liver injury.  Eight weeks after
     lethal irradiation and BMT, recipients were stratified into two groups:
     BMT alone (n = 5) and BMT + Ad-muPA (n= 10).  Both groups of animals were
     bled before (t = 0) and at 2, 4, 8, and 16 weeks after Ad-muPA
       ***administration***  , and the   ***serum***   samples were assessed for
     hAAT by enzyme-linked immunosorbent assay.  RESULTS: Transgenic donor mice
     expressed 5 to 10 mg/mL of hAAT.  Recipients of BMT alone expressed less
     than 80 ng/mL of hAAT over all time periods.  Animals receiving BMT +
     Ad-muPA showed sustained and stable hAAT expression of approximately 200
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ng/mL. Differences were statistically significant at each time point. CONCLUSION: ***Serum*** protein ***levels*** from liver-specific transgene expression are detectable and persist after BMT. Expression is low, but inducible with liver injury. We are currently developing strategies to augment donor-derived, liver-specific protein expression after BMT.

L24 ANSWER 2 OF 60 MEDLINE on STN
AN 2004398251 MEDLINE
DN PubMed ID: 15301559
TI Augmentation therapy for alpha(1)-antitrypsin ***deficiency*** .
AU Juvelekian Georges S; Stoller James K
CS Department of Pulmonary, Allergy, and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
SO Drugs, ***(2004)*** Vol. 64, No. 16, pp. 1743-56. Ref: 47
Journal code: 7600076. ISSN: 0012-6667.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200412
ED Entered STN: 11 Aug 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 7 Dec 2004
AB ***alpha*** (***1***)- ***Antitrypsin*** (AAT) ***deficiency*** is a common but under-recognised condition. Since its first description by Laurell and Eriksson in 1963, significant advances have been made in understanding the genetics, physiology and pathophysiology of this condition. The ***intravenous*** ***administration*** of purified AAT to AAT- ***deficient*** individuals has been shown to confer biochemical efficacy by raising the ***serum*** AAT ***level*** above an epidemiologically established 'protective threshold' while preserving the biochemical properties and functional capacity of the protease inhibitor. Although the lack of a large randomised controlled trial to date has precluded the definitive demonstration of clinical efficacy of ***intravenous*** AAT augmentation therapy, substantial evidence supporting its use in AAT- ***deficient*** individuals with moderate airflow obstruction has accumulated. For example, both large observational studies comparing rates of forced expiratory volume decline among recipients of augmentation therapy versus non-recipients have shown slower rates of decline among augmentation therapy recipients, especially those with moderately severe airflow obstruction. Also, some evidence suggests that use of augmentation therapy confers an anti-inflammatory effect. For example, a web-based survey suggested that recipients of augmentation therapy experienced fewer respiratory infections than non-recipients.Despite its high cost, ***intravenous*** AAT augmentation therapy remains the only US FDA-approved treatment option for patients with AAT ***deficiency*** . Research into new and evolving treatments is currently underway.

L24 ANSWER 3 OF 60 MEDLINE on STN
AN 2004335288 MEDLINE
DN PubMed ID: 15187777
TI Lack of effect of oral 4-phenylbutyrate on ***serum*** ***alpha*** - ***1*** - ***antitrypsin*** in patients with ***alpha*** - ***1*** - ***antitrypsin*** ***deficiency*** : a preliminary study.
AU Teckman Jeffrey H
CS Department of Pediatrics, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, Missouri, USA.. teckman@wustl.edu
NC M01RR00036 (NCRR)
R03DK56154 (NIDDK)

SO Journal of pediatric gastroenterology and nutrition, ***(2004 Jul)***
Vol. 39, No. 1, pp. 34-7.
Journal code: 8211545. ISSN: 0277-2116.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 8 Jul 2004
Last Updated on STN: 14 Jan 2005
Entered Medline: 13 Jan 2005
AB OBJECTIVE: In homozygotes with ZZ genotype ***alpha*** - ***1*** - ***antitrypsin*** (alpha1AT) ***deficiency*** , mutant alpha1ATZ protein (alpha1ATZ) accumulates in hepatocytes, rather than being secreted into the blood. Homozygous individuals experience emphysema as a result of reduced ***levels*** of circulating alpha1AT in the lung with which to inhibit connective tissue breakdown. Homozygotes may also experience liver disease from the accumulation of alpha1ATZ within hepatocytes, which causes liver damage. A previous study indicated that the compound 4-phenylbutyrate (4-PBA) mediated a significant increase in release of alpha1ATZ from cells in tissue culture and in a mouse model of alpha1AT ***deficiency*** . The authors hypothesized that 4-PBA could be used to treat both the liver and lung disease of humans with alpha1AT ***deficiency*** . METHODS: In this preliminary, open label study the authors evaluated the effect of 14 days of oral 4-PBA therapy on alpha1AT blood ***levels*** in 10 patients with alpha1AT ***deficiency*** . RESULTS: There was no significant increase in alpha1AT blood ***level*** associated with 4-PBA ***administration*** . Symptomatic and metabolic side effects were significant. CONCLUSION: 4-PBA did not increase alpha1AT blood ***levels*** in humans with alpha1AT ***deficiency*** in this preliminary trial.

L24 ANSWER 4 OF 60 MEDLINE on STN
AN 2004022627 MEDLINE
DN PubMed ID: 14720074
TI Delivery systems for pulmonary gene therapy.
AU Gautam Ajay; Waldrep Clifford J; Densmore Charles L
CS Department of Molecular Physiology and Biophysics, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.
SO American journal of respiratory medicine : drugs, devices, and other interventions, ***(2002)*** Vol. 1, No. 1, pp. 35-46. Ref: 127
Journal code: 101132974. ISSN: 1175-6365.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200505
ED Entered STN: 15 Jan 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 5 May 2005
AB Delivery of therapeutic genes to the lungs is an attractive strategy to correct a variety of pulmonary dysfunctions such as cystic fibrosis, ***alpha*** - ***1*** ***antitrypsin*** ***deficiency*** , pulmonary hypertension, asthma, and lung cancer. Different delivery routes such as intratracheal instillation, aerosol and ***intravenous*** injection have been utilized with varying degrees of efficiency. Both viral and non-viral vectors, with their respective strengths and weaknesses, have achieved significant ***levels*** of transgene expression in the lungs. However, the application of gene therapy for the treatment of pulmonary disease has been handicapped by various barriers to the delivery vectors such as ***serum*** proteins during

intravenous delivery, and surfactant proteins and mucus in the airway lumen during topical application of therapeutic genes. Immune and cytokine responses against the delivery vehicle are also major problems encountered in pulmonary gene therapy. Despite these shortcomings much progress has been made to enhance the efficiency, as well as lower the toxicity of gene therapy vehicles in the treatment of pulmonary disorders such as cystic fibrosis, lung cancer and asthma.

L24 ANSWER 5 OF 60 MEDLINE on STN
AN 2003283063 MEDLINE
DN PubMed ID: 12728289
TI Tailored pharmacokinetic dosing allows self- ***administration*** and reduces the cost of IV augmentation therapy with human ***alpha*** (***1***)- ***antitrypsin*** .
AU Piitulainen Eeva; Bernspang Elisabeth; Bjorkman Sven; Berntorp Erik
CS Department of Respiratory Medicine, Malmo University Hospital, Lund University, 20502, Malmo, Sweden.. eeva.piitulainen@lung.mas.lu.se
SO European journal of clinical pharmacology, ***(2003 Jun)*** Vol. 59, No. 2, pp. 151-6. Electronic Publication: 2003-05-01.
Journal code: 1256165. ISSN: 0031-6970.
CY Germany: Germany, Federal Republic of
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200309
ED Entered STN: 18 Jun 2003
Last Updated on STN: 1 Oct 2003
Entered Medline: 30 Sep 2003
AB OBJECTIVE: Severe ***alpha*** (***1***)- ***Antitrypsin*** (AAT) ***deficiency*** (PiZZ) predisposes to the development of emphysema. ***Intravenous*** augmentation therapy with purified human AAT has been available since 1988. The dosage has varied from 60 mg/kg body weight once weekly to 250 mg/kg once monthly. We have found the dosage of 120 mg/kg every 2 weeks to be the most convenient for the patients. The treatment is very expensive. The objective of this investigation was to study whether tailored pharmacokinetic dosing of human AAT allows self- ***administration*** and reduces the total annual dose and cost of ***intravenous*** augmentation therapy. METHODS: Five PiZZ individuals receiving purified human AAT at a dose of 120 mg/kg every 2 weeks were included in the study. Three patients had a percutaneous and one patient had a subcutaneous ***intravenous*** injection port system. After a 4-week interruption of the treatment an ordinary dose of 120 mg/kg human AAT was infused. ***Plasma*** AAT ***levels*** were determined preinfusion, postinfusion, and once daily for 10-14 days. The pharmacokinetic parameters of exogenous AAT were calculated for each patient. Based on these, individual dosage schemes were designed by computer simulation. The patients were treated with the new dose twice weekly for 4 weeks, and ***plasma*** AAT was determined immediately before the last two infusions. RESULTS: At a dose of 1 or 2 g twice weekly the median annual consumption of human AAT was reduced from 286 to 156 g/patient. The trough ***plasma*** AAT ***level*** was maintained above 0.70 g/l, which is considered as protective. The three patients who had an implanted percutaneous venous port system learned to ***administer*** the treatment by themselves at home. The other two patients were treated at home by the district nurse. CONCLUSIONS: The results of our study indicate that tailored pharmacokinetic dosing of human AAT reduces the total annual dose and cost of IV augmentation therapy. In addition, this dosing facilitates self- ***administration*** of AAT and allows treatment at home.

L24 ANSWER 6 OF 60 MEDLINE on STN

AN 2000481450 MEDLINE
DN PubMed ID: 10965494
TI Toxicity associated with repeated administration of first-generation adenovirus vectors does not occur with a helper-dependent vector.
AU O'Neal W K; Zhou H; Morral N; Langston C; Parks R J; Graham F L; Kochanek S; Beaudet A L
CS Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA.. woneal@email.unc.edu
NC HL51754 (NHLBI)
SO Molecular medicine (Cambridge, Mass.), ***(2000 Mar)*** Vol. 6, No. 3, pp. 179-95.
Journal code: 9501023. ISSN: 1076-1551.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 19 Oct 2000
Last Updated on STN: 19 Oct 2000
Entered Medline: 6 Oct 2000
AB BACKGROUND: Certain gene therapy protocols may require multiple ***administrations*** of vectors to achieve therapeutic benefit to the patient. This may be especially relevant for vectors such as adenoviral vectors that do not integrate into the host chromosome. Because immunocompetent animal models used for gene transfer studies develop neutralizing antibodies to adenoviral vectors after a single ***administration*** , little is known about how repeat ***administrations*** of vectors might affect transgene expression and vector toxicity. MATERIALS AND METHODS: We used mice ***deficient*** in the membrane spanning region of immunoglobulin (IgM), which do not develop antibodies, to evaluate the effect of repeated ***intravenous*** ***administration*** of first-generation and helper-dependent adenoviral vectors expressing human ***alpha*** ***1*** - ***antitrypsin*** (hAAT). The duration and ***levels*** of transgene expression were evaluated after repeated ***administration*** of vectors. Toxicity was assessed by measuring the ***level*** of liver enzymes in the ***serum*** and the degrees of hepatocyte hypertrophy and proliferation. RESULTS: We found that previous ***administration*** of first-generation adenoviral vectors can alter the response to subsequent doses. These alterations included an increase in transgene expression early (within 1 and 3 days), followed by a rapid drop in expression by day 7. In addition, previous ***administrations*** of first-generation vectors led to an increase in toxicity of subsequent doses, as indicated by a rise in liver enzymes and an increase in hepatocyte proliferation. In contrast to first-generation vectors, use of the helper-dependent adenovirus vector, Ad-STK109, which contained no viral coding regions, did not lead to increased toxicity after multiple ***administrations*** . CONCLUSIONS: We conclude that the response of the host to adenoviral vectors can be altered after repeated ***administration*** , compared with the response after the initial vector dose. In addition, these experiments provide further evidence for the relative safety of helper-dependent adenoviral vectors for gene therapy, compared with first-generation vectors.

L24 ANSWER 7 OF 60 MEDLINE on STN
AN 2000006193 MEDLINE
DN PubMed ID: 10536068
TI Serine proteinase inhibitor therapy in alpha(1)-antitrypsin inhibitor ***deficiency*** and cystic fibrosis.
AU Doring G
CS Department of General and Environmental Hygiene, Hygiene-Institut, University of Tubingen, Germany.. gerd.doering@uni-tuebingen.de

SO Pediatric pulmonology, ***(1999 Nov)*** Vol. 28, No. 5, pp. 363-75.
Ref: 174
Journal code: 8510590. ISSN: 8755-6863.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 13 Jan 2000
Last Updated on STN: 13 Jan 2000
Entered Medline: 9 Dec 1999
AB Proteinase-antiproteinase imbalances are recognized in several diseases including the two most common lethal hereditary disorders of white populations, ***alpha*** (***1***)- ***antitrypsin*** (alpha(1)-AT) ***deficiency*** and cystic fibrosis (CF). In alpha(1)-AT ***deficiency*** , the type Z variant of alpha(1)-AT forms polymers in the endoplasmic reticulum of hepatocytes resulting in liver disease in childhood. The block in alpha(1)-AT processing in hepatocytes significantly reduces ***levels*** of circulating alpha(1)-AT. This may lead in young adults to panacinar emphysema due to insufficient protection of the lower respiratory tract from neutrophil elastase, permitting progressive destruction of the alveoli. In CF, chronic bacterial lung infections due to impaired mucociliary clearance lead to a vigorous influx of neutrophils in the airways. Released ***levels*** of neutrophil serine proteinases, particularly elastase, exceed the antiproteinase capacity of endogenous serine proteinase inhibitors in the airways. Progressive proteolytic impairment of multiple defense pathways in addition to endobronchial obstruction and airway wall destruction are thought to be responsible for the reduced life expectancy in CF patients. Strategies to augment the antiproteinase defenses in the airways of patients with severe alpha(1)-AT ***deficiency*** or CF include the ***intravenous*** or aerosol ***administration*** of serine proteinase inhibitors. Studies in both patient groups using ***plasma*** -derived or transgenic alpha(1)-AT, recombinant secretory leukoprotease inhibitor or synthetic elastase inhibitors show promising results concerning drug safety and efficacy.

L24 ANSWER 8 OF 60 MEDLINE on STN
AN 1999366420 MEDLINE
DN PubMed ID: 10437367
TI [Alpha 1-protease inhibitor ***deficiency*** . Diagnosis, follow-up and therapy options].
Alpha-1-Proteinaseninhibitor-Mangel. Diagnostik, Krankheitsverlauf und Therapieoptionen.
AU Kohnlein T; Klein H; Welte T
CS Klinik fur Kardiologie, Angiologie und Pneumologie, Otto-von-Guericke-Universitat Magdeburg.. Thomas.Koehnlein@medizin.uni-magdeburg.de
SO Medizinische Klinik (Munich, Germany : 1983), ***(1999 Jul 15)*** Vol. 94, No. 7, pp. 371-6. Ref: 51
Journal code: 8303501. ISSN: 0723-5003.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA German
FS Priority Journals
EM 199909
ED Entered STN: 25 Sep 1999
Last Updated on STN: 25 Sep 1999
Entered Medline: 10 Sep 1999
AB DEFINITION: ***Alpha*** - ***1*** ***antitrypsin*** (alpha-1

proteinase inhibitor) ***deficiency*** is characterized by a marked reduction of ***alpha*** - ***1*** ***antitrypsin*** , the major antiprotease in man. PREVALENCE: ***Alpha*** - ***1*** ***antitrypsin*** ***deficiency*** is one of the most common hereditary diseases in Caucasians of European descent. ***Alpha*** - ***1*** ***antitrypsin*** ***deficiency*** is the underlying disorder in approximately 2% of all patients with chronic obstructive pulmonary disease and lung emphysema. CLINICAL MANIFESTATIONS: Young adults by the age of 30 to 45 years have a high risk for the development of lung emphysema with cough, sputum expectoration and respiratory insufficiency. There is a moderate risk of liver disease. DIAGNOSTIC PROCEDURES AND TREATMENT: The diagnosis is obtained by measurement of ***alpha*** - ***1*** ***antitrypsin*** ***serum*** ***levels*** . Recognition of the disorder is important to prevent deterioration of the pulmonary function by early initiation of preventive measures and treatment. Therapeutic options are physiotherapy, antiobstructive medication and antibiotics. The most direct approach is the ***intravenous*** augmentation therapy with purified ***alpha*** - ***1*** ***antitrypsin*** .

L24 ANSWER 9 OF 60 MEDLINE on STN
AN 1999064098 MEDLINE
DN PubMed ID: 9847632
TI [Long-term therapy of alpha 1-antitrypsin- ***deficiency*** -associated pulmonary emphysema with human alpha 1-antitrypsin].
Langzeittherapie des alpha 1-Antitrypsin-mangelassoziierten Lungenemphysems mit humanem alpha 1-Antitrypsin.
AU Wencker M; Banik N; Buhl R; Seidel R; Konietzko N
CS Ruhrlandklinik, Zentrum fur Pneumologie und Thoraxchirurgie, Essen.
SO Pneumologie (Stuttgart, Germany), ***(1998 Oct)*** Vol. 52, No. 10, pp. 545-52.
Journal code: 8906641. ISSN: 0934-8387.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199902
ED Entered STN: 11 Mar 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 24 Feb 1999
AB ***alpha*** ***1*** - ***antitrypsin*** (alpha 1-AT) ***deficiency*** is a genetic disorder characterized by low ***serum*** ***levels*** of alpha 1-AT and a high risk of pulmonary emphysema at a young age. The resulting surplus of proteases, mainly of neutrophil elastase, can be balanced by i.v. augmentation with alpha 1-AT. However, it is not clear if affected patients benefit from long-term augmentation therapy and no long-term safety data are available. We examined 443 patients with severe alpha 1-AT ***deficiency*** and pulmonary emphysema receiving weekly i.v. infusions of 60 mg/kg body weight alpha 1-AT in addition to their regular medication. The progression of the disease was assessed by repeated lung function measurements, particularly the decline in forced expiratory volume in 1 second (delta FEV1). 443 patients with alpha 1-AT ***deficiency*** tolerated augmentation therapy well with few adverse reactions. The delta FEV1 in 287 patients with available follow-up data was 57.1 +/- 31.1 ml per year. Stratified for baseline FEV1, the decline was 35.6 +/- 21.3 ml in the 108 patients with an initial FEV1 < 30% and 64.0 +/- 26.4 ml in the 164 with 30% < FEV1 < or = 65% of predicted normal (p = 0.0008). The remaining 15 patients had an initial FEV1 > 65%. Long-term treatment with i.v. ***alpha*** ***1*** - ***antitrypsin*** in patients with severe alpha 1-Pi ***deficiency*** is feasible and safe. The decline in forced expiratory volume in one second is related to the initial forced

expiratory volume in one second as in ***alpha*** ***1*** - ***antitrypsin*** ***deficient*** patients not receiving augmentation therapy.

L24 ANSWER 10 OF 60 MEDLINE on STN
AN 1998302248 MEDLINE
DN PubMed ID: 9638392
TI Alpha 1-antitrypsin. Hope on the horizon for emphysema sufferers?.
AU Schwaiblmair M; Vogelmeier C
CS Department of Internal Medicine, Klinikum Grosshadern, University of Munich, Germany.
SO Drugs & aging, ***(1998 Jun)*** Vol. 12, No. 6, pp. 429-40. Ref: 145
Journal code: 9102074. ISSN: 1170-229X.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 10 Sep 1998
Last Updated on STN: 10 Sep 1998
Entered Medline: 3 Sep 1998
AB ***Alpha*** ***1*** - ***Antitrypsin*** (alpha 1AT) ***deficiency*** is the most common genetic cause of liver disease in children and emphysema in adults. Therapy for pulmonary disease attributable to alpha 1AT ***deficiency*** includes alpha 1AT augmentation therapy along with supportive measures. The alpha 1AT preparation that is currently used for therapy is derived from fractionated ***plasma*** . The results of clinical trials suggest that augmentation therapy with alpha 1AT slows the progression of emphysema and causes few adverse events. Patients with ***plasma*** ***levels*** of alpha 1AT that are < 11 mumol/L and who have airway obstruction should be considered for augmentation therapy. Novel approaches include the ***administration*** of aerosolised alpha 1AT, recombinant alpha 1AT, gene therapy and synthetic elastase inhibitors.

L24 ANSWER 11 OF 60 MEDLINE on STN
AN 1998151604 MEDLINE
DN PubMed ID: 9490904
TI Mitochondrial neurogastrointestinal encephalomyopathy presenting with protein-losing gastroenteropathy and serum copper ***deficiency*** : a case report.
AU Hamano H; Ohta T; Takekawa Y; Kouda K; Shinohara Y
CS Department of Neurology, Tokai University School of Medicine.
SO Rinsho shinkeigaku = Clinical neurology, ***(1997 Oct)*** Vol. 37, No. 10, pp. 917-22. Ref: 20
Journal code: 0417466. ISSN: 0009-918X.
CY Japan
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA Japanese
FS Priority Journals
EM 199804
ED Entered STN: 30 Apr 1998
Last Updated on STN: 30 Apr 1998
Entered Medline: 21 Apr 1998
AB We report a 56-year old female with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), presenting with protein-losing gastroenteropathy and ***serum*** copper ***deficiency*** . There was no neuromuscular disease in her family members. Three years prior to admission, she developed severe gastrointestinal symptoms including

diarrhea, nausea, vomiting and ascites, and was diagnosed as having protein-losing gastroenteropathy based on ***alpha*** (***1***)-***antitrypsin*** clearance and other tests. She was referred to our department when neurological symptoms were apparent. Neurological examinations revealed bilateral ptosis, ophthalmoplegia, hearing loss, facial and limb muscle weakness, mild sensory deficit of vibration on her feet and hypoactive deep tendon reflexes. Pigmentary retinopathy, cerebellar ataxia and heart block were not seen. ***Serum*** copper ***level*** was decreased to 45 micrograms/dl (normal: 83-155). Chronic intestinal pseudo-obstruction was proven by X-ray studies, and diffuse leukoencephalopathy demonstrated on brain MRI. On EMG, motor nerve conduction velocities were prolonged with temporal dispersion. Her muscle biopsy from biceps brachii muscle showed both neuropathic and myopathic changes, scattered ragged-red fibers and focal cytochrome c oxidase ***deficiency*** . Southern blot and polymerase chain reaction analysis on mitochondrial DNA showed no deletions nor point mutations. The clinical and pathologic findings of the present patient fulfilled the diagnostic criteria of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) proposed by Hirano et al. There are few reported patients with MNGIE in Japan, but none presented with protein-losing gastroenteropathy and ***serum*** copper ***deficiency*** . Since the copper is a cofactor of cytochrome c oxidase, decreased ***serum*** copper ***level*** may aggravate the respiratory chain enzyme metabolism in mitochondria. Therefore, treatment for gastrointestinal tract disturbance and copper ***administration*** may be necessary to prevent disease progression.

L24 ANSWER 12 OF 60 MEDLINE on STN
AN 1998029419 MEDLINE
DN PubMed ID: 9363132
TI Lung disease due to alpha 1-antitrypsin ***deficiency*** .
AU Wiedemann H P; Stoller J K
CS Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, OH 44195, USA.
SO Current opinion in pulmonary medicine, ***(1996 Mar)*** Vol. 2, No. 2, pp. 155-60. Ref: 44
Journal code: 9503765. ISSN: 1070-5287.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 9 Jan 1998
Last Updated on STN: 9 Jan 1998
Entered Medline: 2 Dec 1997
AB The association between ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** and heritable emphysema was discovered in 1963. Subsequent epidemiologic evidence suggested that a ***serum*** ***alpha*** ***1*** - ***antitrypsin*** ***level*** of 11 mumol/L (about 80 mg/dL by the still-used "commercial standard"), which is about 35% of the normal ***level*** , represents a "threshold" value, below which the risk of developing emphysema is increased and above which the emphysema risk is not increased. Recently, the ability to isolate and purify the ***alpha*** ***1*** - ***antitrypsin*** protein from human blood has made "specific" augmentation therapy possible. ***Intravenous*** infusion of ***alpha*** ***1*** - ***antitrypsin*** raises ***serum*** and alveolar ***levels*** above the putative thresholds, but clinical efficacy (i.e., decreased rate of decline in lung function and/or improved survival) remains presumptive. Based on available evidence, the American Thoracic Society recommends augmentation therapy for individuals with both a documented severe

deficiency of ***alpha*** ***1*** - ***antitrypsin*** and fixed airflow obstruction.

L24 ANSWER 13 OF 60 MEDLINE on STN
AN 97088293 MEDLINE
DN PubMed ID: 8934231
TI Evidence for the systemic delivery of a transgene product from salivary glands.
AU Kagami H; O'Connell B C; Baum B J
CS Clinical Investigations and Patient Care Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892-1190, USA.
SO Human gene therapy, ***(1996 Nov 10)*** Vol. 7, No. 17, pp. 2177-84.
Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 13 Mar 1997
Last Updated on STN: 13 Mar 1997
Entered Medline: 3 Mar 1997
AB The aim of this study was to assess the feasibility of using gene transfer to salivary glands to direct the systemic delivery of therapeutic proteins in vivo. We used a replication- ***deficient*** recombinant adenovirus vector (Ad alpha 1AT) that encodes human ***alpha*** ***1*** - ***antitrypsin*** (h alpha 1-AT), which we used as a marker protein. Ad alpha 1AT (5 x 10(9) pfu) was ***administered*** by retrograde ductal instillation to the submandibular glands of male rats. The amount of h alpha 1-AT found in the salivary glands, saliva, ***serum*** , and other tissues was analyzed by a sensitive enzyme-linked immunosorbent assay (ELISA). Maximal ***levels*** of the marker protein were detected at 24-48 hr post-virus ***administration*** for glands (274 ng/mg protein), saliva (approximately 313 ng/ml), and ***serum*** (approximately 5 ng/ml). ***Serum*** ***levels*** remained elevated for 96 hr, whereas the measured half-life for the marker protein was approximately 2 hr. Generally little to no h alpha 1-AT was detectable in most other organs. However, we were able to measure low ***levels*** of marker protein in tissues immediately surrounding infected glands. In all animals studied, ***levels*** of h alpha 1-AT were higher in the glandular venous effluent than in arterial blood. Similar results were found with parotid glands. The aggregate data demonstrate that salivary glands may be a target for the nonsurgical, systemic delivery of transgene-encoded therapeutic proteins for diseases that require relatively low circulating protein ***levels*** .

L24 ANSWER 14 OF 60 MEDLINE on STN
AN 96310240 MEDLINE
DN PubMed ID: 8732898
TI Iron ***deficiency*** and intestinal malabsorption in HIV disease.
AU Castaldo A; Tarallo L; Palomba E; Albano F; Russo S; Zuin G; Buffardi F; Guarino A
CS Department of Pediatrics, University Federico II, Naples, Italy.
SO Journal of pediatric gastroenterology and nutrition, ***(1996 May)*** Vol. 22, No. 4, pp. 359-63.
Journal code: 8211545. ISSN: 0277-2116.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199609
ED Entered STN: 8 Oct 1996

Last Updated on STN: 3 Feb 1997
Entered Medline: 26 Sep 1996

AB Children with human immunodeficiency virus (HIV) infection have a higher prevalence of intestinal malabsorption. Anemia is also a common feature in these children. The aims of this work were (a) to establish the prevalence of iron ***deficiency*** in HIV-infected children, (b) to test the hypothesis that iron ***deficiency*** is related to intestinal malabsorption, (c) to see whether it may contribute to anemia, and (d) to evaluate the sensitivity of oral iron load in the investigation of intestinal function. To accomplish these goals, 71 HIV-infected symptomatic children were enrolled. Iron ***serum*** values were determined before and after oral load with ferrous sulfate. The correlation between basal and post-load iron ***levels*** was evaluated by linear regression. Xylose ***level*** after oral load, fecal fat, and fecal ***alpha*** ***1*** - ***antitrypsin*** concentration were also determined. Iron ***deficiency*** was detected in 48% of patients, and it was significantly associated with intestinal iron malabsorption. Sugar malabsorption, steatorrhea, and fecal protein loss were detected in 26, 36, and 17% of patients, respectively. Low hemoglobin ***levels*** were detected in 66% of patients. The majority of children with iron ***deficiency*** also had anemia. Preliminary data showed that oral iron ***administration*** was sufficient for raising hemoglobin in children with normal iron absorption, whereas parenteral ***administration*** was required in those with iron malabsorption. We conclude that (a) iron ***deficiency*** is a major feature of pediatric HIV infection, (b) it is related to intestinal malabsorption, and (c) it contributes to anemia. Finally, oral iron load is a sensitive test for investigating intestinal function.

L24 ANSWER 15 OF 60 MEDLINE on STN
AN 95292722 MEDLINE
DN PubMed ID: 7774374
TI Failure to achieve adequate ***serum*** ***levels*** with monthly replacement therapy in ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** .
AU Cammarata S K; Stone C L; Carey J L; Eichenhorn M S
SO Chest, ***(1994 Aug)*** Vol. 106, No. 2, pp. 651-2.
Journal code: 0231335. ISSN: 0012-3692.
CY United States
DT Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199507
ED Entered STN: 20 Jul 1995
Last Updated on STN: 20 Jul 1995
Entered Medline: 11 Jul 1995

L24 ANSWER 16 OF 60 MEDLINE on STN
AN 95128527 MEDLINE
DN PubMed ID: 7827760
TI [Evaluation of replacement therapy in emphysema caused by alpha 1-antitrypsin ***deficiency***].
Evaluacion del tratamiento sustitutivo del enfisema por deficit de alfa-1-antitripsina.
AU Miravitlles M; Vidal R; Torrella M; Bofill J M; Cotrina M; de Gracia J
CS Servicio de Neumologia, Hospital General Universitario Vall d'Hebron, Barcelona.
SO Archivos de bronconeumologia, ***(1994 Dec)*** Vol. 30, No. 10, pp. 479-84.
Journal code: 0354720. ISSN: 0300-2896.
CY Spain

DT Journal; Article; (JOURNAL ARTICLE)
LA Spanish
FS Priority Journals
EM 199502
ED Entered STN: 7 Mar 1995
Last Updated on STN: 7 Mar 1995
Entered Medline: 23 Feb 1995
AB Assessment of ***alpha*** ***1*** - ***antitrypsin*** replacement therapy (AAT) for emphysema. Patient characteristics were analyzed along with the possible side effects of the treatment and its efficacy in maintaining appropriate AAT blood ***levels*** . Lung function changes were also studied. The treatment protocol began with 4 weekly ***intravenous*** doses of 60 mg/kg AAT (***Prolastin***) and continued with monthly doses of 240 mg/kg. AAT ***serum*** ***levels*** were measured before each dose. Every 6 months pulmonary function tests (spirometry, plethysmography and CO transfer) were performed. Thirteen patients (mean age 46 yr) have been studied since 1988. Mean initial FEV1 was 0.79 l. Over 250 doses have been infused with no significant side effects reported. AAT ***levels*** before treatment in 3 patients were lower than that considered protective (50 mg/dl). Function tests results indicated stabilization of spirometric values in most cases. Diagnosis of AAT ***deficiency*** is delayed considerably, meaning that significant functional deterioration takes place before replacement therapy begins. No side effects of treatment have been observed. Until an appropriate interval between doses has been established, each patient's AAT ***levels*** must be monitored.

L24 ANSWER 17 OF 60 MEDLINE on STN
AN 94201564 MEDLINE
DN PubMed ID: 8151119
TI Ex vivo and in vivo gene transfer to the skin using replication-***deficient*** recombinant adenovirus vectors.
AU Setoguchi Y; Jaffe H A; Danel C; Crystal R G
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.
SO The Journal of investigative dermatology, ***(1994 Apr)*** Vol. 102, No. 4, pp. 415-21.
Journal code: 0426720. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199405
ED Entered STN: 23 May 1994
Last Updated on STN: 23 May 1994
Entered Medline: 6 May 1994
AB The skin has the potential for a variety of gene therapy applications. In addition to local delivery, it is the largest organ of the body, and highly vascular, and thus is an ideal site for systemic delivery of gene products. To evaluate the potential for adenovirus-mediated skin gene transfer, the replication- ***deficient*** recombinant adenovirus vectors Ad.RSV beta gal (coding for Escherichia coli beta-galactosidase) and Ad alpha 1AT (coding for human ***alpha*** ***1*** - ***antitrypsin***) were used in both ex vivo and in vivo approaches. Following in vitro infection with Ad.RSV beta gal, murine keratinocytes expressed beta-galactosidase. Parallel in vitro studies with Ad alpha 1AT documented de novo synthesis and secretion of human alpha 1AT as shown by [35S]methionine labeling and immunoprecipitation. Quantification of human alpha 1AT in the culture supernatants demonstrated 0.1-0.3 microgram human alpha 1AT secreted/ml-24 h. Evaluation of the ***serum*** of mice receiving transplants (10(5) cells/mouse) of Ad alpha 1AT-infected syngeneic keratinocytes demonstrated human alpha 1AT for at least 14 d

with maximum ***levels*** of 41 ng/ml. To demonstrate the feasibility of direct adenovirus-mediated in vivo transfer of genes to the skin, Ad.RSV beta gal or Ad alpha 1AT were ***administered*** subcutaneously to mice. Histologic evaluation after 4 d demonstrated expression of beta-galactosidase in various types of skin cells. Quantification of human alpha 1AT in ***serum*** of animals infected subcutaneously with Ad alpha 1AT showed ***levels*** of 53 ng/ml at day 4, with human alpha 1AT detectable for at least 14 d. These observations support the feasibility of ex vivo and in vivo gene transfer to the skin mediated by replication- ***deficient*** adenovirus vectors.

L24 ANSWER 18 OF 60 MEDLINE on STN
AN 94183574 MEDLINE
DN PubMed ID: 8136153
TI Intraperitoneal in vivo gene therapy to deliver alpha 1-antitrypsin to the systemic circulation.
AU Setoguchi Y; Jaffe H A; Chu C S; Crystal R G
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892.
SO American journal of respiratory cell and molecular biology, ***(1994*** *** Apr)*** Vol. 10, No. 4, pp. 369-77.
Journal code: 8917225. ISSN: 1044-1549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199404
ED Entered STN: 9 May 1994
Last Updated on STN: 9 May 1994
Entered Medline: 28 Apr 1994
AB The utility of replication- ***deficient*** recombinant adenovirus vector-mediated transfer and expression of the ***alpha*** ***1*** - ***antitrypsin*** (alpha 1AT) cDNA to peritoneal mesothelial tissues was evaluated as a means of delivering alpha 1AT to the systemic circulation. Preliminary studies with Ad.RSV beta gal, an adenovirus vector expressing the Escherichia coli lacZ gene (beta-galactosidase), showed that intraperitoneal injection of 10(9) plaque-forming units (pfu) to cotton rats resulted in beta-galactosidase activity in mesothelial cells lining the peritoneal cavity. After intraperitoneal ***administration*** of 10(9) pfu of Ad alpha 1AT (an adenovirus vector containing the human alpha 1AT cDNA), human alpha 1AT was detectable in ***serum*** for up to 24 days, with a maximal ***level*** of 3.4 micrograms/ml at 4 days. Expression of the exogenous gene was localized to the peritoneal mesothelium as PCR analyses detected no evidence of expression of the exogenous gene in any other tissues evaluated. Anti-adenovirus vector antibodies were detectable in ***serum*** after intraperitoneal ***administration*** of the recombinant vectors, including antibodies with neutralizing activity. Repeat ***administrations*** of adenovirus vectors to the peritoneal cavity at 1 wk and 1 mo after the initial dose failed to show gene expression, but repeat ***administration*** 3 mo after demonstrated measurable gene transfer and expression. Together these observations suggest replication- ***deficient*** adenovirus-mediated gene transfer to the peritoneal mesothelium offers a promising means to transfer alpha 1AT to the systemic circulation, although immunity induced against the adenovirus may limit frequent repetitive dosing.

L24 ANSWER 19 OF 60 MEDLINE on STN
AN 94169920 MEDLINE
DN PubMed ID: 8124298
TI Studies on lymphocyte characteristics in patients with homozygous alpha 1-proteinase inhibitor ***deficiency*** during substitution therapy.

AU Schoenfeld N; Schmitt M; Remy N; Wahn U; Loddenkemper R
CS Dept of Pulmonary Medicine II, Chest Hospital Heckeshorn, Berlin, Germany.
SO Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica tisiologica e malattie apparato respiratorio, Universita di Napoli, Secondo ateneo, ***(1993 Dec)*** Vol. 48, No. 6, pp. 613-6.
Journal code: 9307314. ISSN: 1122-0643.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199404
ED Entered STN: 20 Apr 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 13 Apr 1994
AB Alpha 1-proteinase inhibitor (alpha 1-PI) has been demonstrated to suppress mitogen-induced lymphocyte response in vitro. To evaluate the effect of ***intravenous*** application of human alpha 1-PI (***Prolastin*** HS) on cellular immunity, we determined total lymphocyte count, lymphocyte subsets and lymphocyte response to concanavalin A, before and 24 h after infusion of 60 mg.kg-1 body weight alpha 1-PI in eight patients with homozygous alpha 1-PI ***deficiency*** (PiZ phenotype). The results were compared with two blood samples from seven healthy controls. After infusion, ***serum*** alpha 1-PI ***levels*** were increased from 0.98 +/- 0.24 to 2.68 +/- 0.51 g.l-1. No significant differences were found for total lymphocyte count, lymphocyte subsets and lymphocyte response between both groups in both samples. Maximum 3H-thymidine incorporation before and after infusion showed no significant difference; the same was true for the two control samples. However, additional incubation in vitro with alpha 1-PI 5 g.l-1 led to a significant ($p < 0.03$) decrease of lymphocyte proliferation in samples after infusion. Our data indicate that alpha 1-PI substitution therapy does not lead to a major suppression of lymphocyte response to concanavalin A in PiZ individuals in vivo, although a suppressive effect was found after additional in vitro incubation with alpha 1-PI.

L24 ANSWER 20 OF 60 MEDLINE on STN
AN 93251028 MEDLINE
DN PubMed ID: 1302034
TI Adenovirus-mediated in vivo gene transfer and expression in normal rat liver.
AU Jaffe H A; Danel C; Longenecker G; Metzger M; Setoguchi Y; Rosenfeld M A; Gant T W; Thorgeirsson S S; Stratford-Perricaudet L D; Perricaudet M; +
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.
SO Nature genetics, ***(1992 Aug)*** Vol. 1, No. 5, pp. 372-8.
Journal code: 9216904. ISSN: 1061-4036.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
ED Entered STN: 18 Jun 1993
Last Updated on STN: 18 Jun 1993
Entered Medline: 9 Jun 1993
AB Replication ***deficient*** , recombinant adenovirus (Ad) vectors do not require target cell replication for transfer and expression of exogenous genes and thus may be useful for in vivo gene therapy in hepatocytes. In vitro, primary cultures of rat hepatocytes infected with a recombinant Ad containing a human ***alpha*** ***1*** - ***antitrypsin*** cDNA (Ad-alpha 1AT) synthesized and secreted human alpha 1AT for 4 weeks. In rats, in vivo intraportal

administration of a recombinant Ad containing the E. coli lacZ gene, was followed by expression of beta-galactosidase in hepatocytes 3 days after infection. Intraportal infusion of Ad-alpha 1AT produced detectable ***serum*** ***levels*** of human alpha 1AT for 4 weeks. Thus, targeted gene expression has been achieved in the liver, albeit at low ***levels*** , suggesting that adenovirus vectors may be a useful means for in vivo gene therapy in liver disorders.

L24 ANSWER 21 OF 60 MEDLINE on STN
AN 92291290 MEDLINE
DN PubMed ID: 1601985
TI Albumin gene expression is down-regulated by albumin or macromolecule infusion in the rat.
AU Pietrangelo A; Panduro A; Chowdhury J R; Shafritz D A
CS Marion Bessin Liver Research Center, Albert Einstein College of Medicine, Bronx, New York 10461.
NC DK-17609 (NIDDK)
P30-DK-41296 (NIDDK)
SO The Journal of clinical investigation, ***(1992 Jun)*** Vol. 89, No. 6, pp. 1755-60.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199207
ED Entered STN: 24 Jul 1992
Last Updated on STN: 24 Jul 1992
Entered Medline: 13 Jul 1992
AB A novel feedback regulatory mechanism operating on transcription of the albumin gene is described in the rat. In 1946, it was proposed that circulating colloids, including ***serum*** albumin, may affect the synthesis and/or secretion of albumin in the liver. The molecular basis for this proposed regulation has now been investigated by adding oncotically active macromolecules to the circulation of normal or genetically albumin- ***deficient*** Nagase analbuminemic rats (NAR) and analyzing the hepatic expression of genes, including albumin after 24 h. The transcription rate of the albumin gene was higher in NAR than in normal rats and was dramatically reduced by raising ***serum*** albumin to 1.6 g/dl. ***Intravenous*** infusion of albumin into normal rats also decreased transcriptional activity of the albumin gene by 50-60%, and this decrease correlated with changes in ***serum*** colloid osmotic pressure after albumin infusion. Inhibition of albumin gene transcription was also observed upon ***intravenous*** infusion of other protein or nonprotein macromolecules, such as gamma-globulin and dextran. This down-regulation appears to control the steady-state ***level*** of albumin mRNA in the liver. Aside from a concomitant decrease in apo E gene transcription after albumin or macromolecule infusion, there was no change in the transcription rate of other genes, including those exhibiting liver-preferred or -specific expression (e.g., tyrosine amino-transferase, cytochrome P-450, ***alpha*** ***1*** - ***antitrypsin*** , apolipoproteins A-I and B, and transferrin) or general cellular expression (e.g., alpha-tubulin, pro alpha 2 collagen, and beta-actin). Feedback regulation of albumin gene expression by ***serum*** colloids may serve as a specific homeostatic mechanism to maintain the steady-state ***level*** of total protein in the circulation.

L24 ANSWER 22 OF 60 MEDLINE on STN
AN 92103056 MEDLINE
DN PubMed ID: 1760450
TI Alpha 1-antitrypsin ***deficiency*** .

AU Ellett M L
SO Gastroenterology nursing : the official journal of the Society of Gastroenterology Nurses and Associates, ***(1991 Dec)*** Vol. 14, No. 3, pp. 138-41.
Journal code: 8915377. ISSN: 1042-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Nursing Journals
EM 199202
ED Entered STN: 2 Mar 1992
Last Updated on STN: 2 Mar 1992
Entered Medline: 12 Feb 1992
AB ***alpha*** ***1*** - ***Antitrypsin*** (AAT) is a polymorphic protein with many variants collectively known as the Pi system. The most common alleles are the M, S and Z, which are co-dominantly inherited. Infants with PiZZ have approximately 16% of the normal AAT ***serum*** concentration. ***alpha*** ***1*** - ***Antitrypsin*** ***deficiency*** (AATD) is an inborn error of metabolism which is principally associated with liver disease in children and emphysema in young adulthood. Individuals with AATD produce an abnormal protein which accumulates in the liver, resulting in decreased ***serum*** ***levels*** . Affected individuals cannot protect their lungs from digestion by elastase. Smoking is a significant risk factor for the early development of emphysema. ***Prolastin*** , human alpha 1-protease inhibitor, is now available as replacement therapy. Weekly ***intravenous*** ***administration*** , with the goal of maintaining the ***serum*** AAT greater than 80 mg/dl, appears to arrest pulmonary damage. Its effect on liver disease is unknown at this time. A recombinant alpha 1-protease inhibitor is being tested in aerosol form with promising early results.

L24 ANSWER 23 OF 60 MEDLINE on STN
AN 90348341 MEDLINE
DN PubMed ID: 2117165
TI Strategies for aerosol therapy of alpha 1-antitrypsin ***deficiency*** by the aerosol route.
AU Hubbard R C; Crystal R G
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.
SO Lung, ***(1990)*** Vol. 168 Suppl, pp. 565-78.
Journal code: 7701875. ISSN: 0341-2040.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199009
ED Entered STN: 26 Oct 1990
Last Updated on STN: 26 Oct 1990
Entered Medline: 20 Sep 1990
AB ***Alpha*** ***1*** - ***antitrypsin*** (AAT) ***deficiency*** is a genetic disease in which low ***serum*** and lung ***levels*** of the antiprotease AAT cause a ***deficiency*** of the anti-elastase defensive screen of the lower respiratory tract such that neutrophil elastase is free to degrade the connective tissue of the lung, eventually resulting in emphysema. ***Intravenous*** AAT infusion therapy restores lung ***levels*** of AAT, but is inefficient, costly and a demanding form of therapy. As an alternative, we evaluated aerosol delivery of human ***plasma*** AAT (pAAT) and recombinant DNA-produced AAT (rAAT), as a means of providing anti-elastase protection to the lower respiratory tract. In vitro studies demonstrated that both pAAT and rAAT can be aerosolized into droplets suitable for alveolar deposition without

loss of antiprotease activity. When ***administered*** by aerosol to individuals with AAT ***deficiency*** , pAAT and rAAT each significantly raised lung epithelial lining fluid ***levels*** of AAT and anti-neutrophil elastase capacity, with the likelihood that twice daily ***administration*** of 100 mg of either form would result in normalization of lung anti-elastase defenses at the alveolar surface. Studies in sheep further demonstrated that the aerosolized pAAT and rAAT were each able to pass through alveolar epithelium and gain access to the interstitial compartment of the lung, thus increasing anti-elastase defenses of the lung interstitium. Therapy was safe and well tolerated in all cases. Aerosol therapy with pAAT or rAAT is a safe, feasible, and likely a biochemically efficacious alternative to ***intravenous*** AAT augmentation therapy and merits further long-term studies for clinical therapy.

L24 ANSWER 24 OF 60 MEDLINE on STN
AN 90284311 MEDLINE
DN PubMed ID: 2191843
TI [Long-term substitution in homozygous ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** . Effect of the proteinase-antiproteinase equilibrium in ***plasma*** and sputum]. Dauersubstitution bei homozygotem ***alpha*** ***1*** - ***Antitrypsin*** -Mangel. Einfluss auf das Proteinasen-Antiproteinasen-Gleichgewicht in ***Plasma*** und Sputum.
AU Braun J; Welle S; van Wees J; Winterhoff R; Wood W G; Dalhoff K; Wiessmann K J
CS Klinik fur Innere Medizin, Medizinische Universitat Lubeck.
SO Deutsche medizinische Wochenschrift (1946), ***(1990 Jun 8)*** Vol. 115, No. 23, pp. 889-94.
Journal code: 0006723. ISSN: 0012-0472.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199007
ED Entered STN: 24 Aug 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 26 Jul 1990
AB Long-term replacement with human ***alpha*** ***1*** - ***antitrypsin*** (60 mg/kg once a week intravenously) was carried out in seven patients with homozygous ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** (7 males, mean age 50.8 [40-59] years) and progressive pulmonary emphysema for an average of 16 (13-20) weeks. After at least 12 weeks' therapy the concentrations of ***alpha*** ***1*** - ***antitrypsin*** , elastase- ***alpha*** ***1*** - ***antitrypsin*** complex, alpha 2-macroglobulin, lactoferrin and elastase inhibition capacity in ***plasma*** and sputum were assayed, these assays being performed before starting the ***alpha*** ***1*** - ***antitrypsin*** infusion and at various times during the following week. After the infusion the ***plasma*** concentration of ***alpha*** ***1*** - ***antitrypsin*** rose from a depressed initial ***level*** (median 1.22 g/l) to a ***level*** approximately five times higher (median after 1 hour: 5.96 g/l, P less than 0.001), and then declined exponentially, though it never fell below the threshold of 35% of normal which is regarded as the protective ***level*** . Elastase inhibition capacity displayed similar changes (r = 0.85). The sputum concentration of ***alpha*** ***1*** - ***antitrypsin*** rose more slowly than the ***plasma*** concentration; from the initial ***level*** (median 8 mg/l) it reached a maximum about four times higher after 24 hours (median 36 mg/l; P less than 0.02). Elastase inhibition capacity rose from 151 mIU/ml (median) before the ***alpha*** ***1*** - ***antitrypsin*** infusion to

450 mIU/ml at 24 hours. These findings suggest that ***alpha*** ***1*** - ***antitrypsin*** replacement will have beneficial effects on proteinase-antiproteinase equilibrium. Determination of elastase inhibition capacity in the sputum is suitable for monitoring dosage during replacement therapy.

L24 ANSWER 25 OF 60 MEDLINE on STN
AN 90207129 MEDLINE
DN PubMed ID: 2138750
TI [Evaluation after 2 years of substitutive treatment of PiZZ emphysema with alpha-1 antitrypsin. 9 cases].
Bilan a deux ans du traitement substitutif de l'emphyseme PiZZ par l'alpha 1-antitrypsine. Neuf cas.
AU Carles P; Constans J; Pujazon M C; Arnaud J; Lauque D; Goudemand M
CS Service de Medecine, Hopital Purpan, Toulouse.
SO Presse medicale (Paris, France : 1983), ***(1990 Mar 24)*** Vol. 19, No. 11, pp. 514-8.
Journal code: 8302490. ISSN: 0755-4982.
CY France
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 199005
ED Entered STN: 1 Jun 1990
Last Updated on STN: 1 Jun 1990
Entered Medline: 7 May 1990
AB Homozygous PiZZ individuals with a ***serum*** ***deficiency*** due to a defect in the secretion of the ***alpha*** ***1*** - ***antitrypsin*** protein are at risk of developing severe panlobular emphysema. Tobacco smokers are particularly exposed to the disease which begins at an earlier age. Treatment by substitutive therapy with ***alpha*** ***1*** - ***antitrypsin*** concentrates seems to be the only possibility. A two years' clinical trial was performed in 9 PiZZ patients, with more than 1,500 infusions being ***administered*** weekly. ***Serum*** AAT ***levels*** were used as guidelines to follow biochemical changes in the protease-antiprotease balance. From 0.16 g/l initially, the AAT ***level*** rose to 0.57 g/l after 7 months. No adverse reaction was observed during the trial; the concentrated protein was well accepted, ant the antielastase activity of the protein recovered after injection was equivalent to the activity injected. An attempt to ***administer*** the infusions monthly was stopped when we observed a dramatic decrease of the ***serum*** AAT ***level*** . Clinically, stabilization of the symptoms was noted. No degradation was observed in the patients who took part in the trial, even if no real improvement was detected.

=> d bib abs 26-60

L25 ANSWER 26 OF 60 MEDLINE on STN
AN 90128848 MEDLINE
DN PubMed ID: 2613191
TI Response of serine antiproteases to growth hormone therapy in growth hormone ***deficient*** children.
AU Schwarzenberg S J; Sharp H L; Freier E F; Seelig S
CS Department of Pediatrics, University of Minnesota, Minneapolis.
NC AM07420 (NIADDK)
AM32817 (NIADDK)
AM34931 (NIADDK)

SO Hormone research, ***(1989)*** Vol. 31, No. 5-6, pp. 221-5.
Journal code: 0366126. ISSN: 0301-0163.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199003
ED Entered STN: 28 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 6 Mar 1990
AB Growth hormone regulates the hepatic mRNA ***levels*** of ***alpha*** ***1*** - ***antitrypsin*** and two contrapsin-like mRNAs in the rat. To determine whether growth hormone regulates similar serine protease inhibitors in humans, we measured ***serum*** ***alpha*** ***1*** - ***antitrypsin*** , alpha 1-antichymotrypsin, and antithrombin III by radioimmunodiffusion in 16 growth hormone ***deficient*** children before and after growth therapy. Of the 19 determinations made, 17/19 showed an increase in ***alpha*** ***1*** - ***antitrypsin*** after ***administration*** of growth hormone, 198.6 +/- 39.1 mg/dl before growth hormone and 239.4 +/- 44 mg/dl after growth hormone (p = 0.005). Specificity of the response for ***alpha*** ***1*** - ***antitrypsin*** was indicated by the fact that neither alpha 1-antichymotrypsin or antithrombin III values changed after growth hormone (p = 0.6 and 0.5, respectively). These data are compatible with the hypothesis that growth hormone regulates serine protease inhibitors in humans and suggests that investigation of other members of the serpin gene family might prove fruitful in defining additional growth hormone target genes.

L25 ANSWER 27 OF 60 MEDLINE on STN
AN 90009332 MEDLINE
DN PubMed ID: 2794066
TI Recombinant DNA-produced ***alpha*** ***1*** - ***antitrypsin*** ***administered*** by aerosol augments lower respiratory tract antineutrophil elastase defenses in individuals with ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** .
AU Hubbard R C; McElvaney N G; Sellers S E; Healy J T; Czerski D B; Crystal R G
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20892.
SO The Journal of clinical investigation, ***(1989 Oct)*** Vol. 84, No. 4, pp. 1349-54.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198911
ED Entered STN: 28 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 1 Nov 1989
AB ***Alpha*** ***1*** - ***Antitrypsin*** (alpha 1AT) ***deficiency*** is characterized by insufficient amounts of alpha 1AT to protect the lower respiratory tract from neutrophil elastase, resulting in emphysema. Yeast-produced recombinant alpha 1AT (rAAT) has normal antielastase function but is associated with high renal clearance, thus obviating chronic ***intravenous*** ***administration*** . As an alternative, we evaluated aerosol ***administration*** of rAAT to alpha 1AT- ***deficient*** individuals. After aerosol ***administration*** of single doses of 10-200 mg of rAAT, epithelial lining fluid (ELF) alpha 1AT antineutrophil elastase defenses were augmented in proportion to the dose of rAAT ***administered*** . ELF

alpha 1AT ***levels*** and antineutrophil elastase capacity 4 h after 200 mg rAAT aerosol were increased 40-fold over preaerosol ***levels*** , and were fivefold increased over baseline at 24 h after aerosol ***administration*** . rAAT was detectable in ***serum*** after aerosol, indicating that the lower respiratory tract epithelium may be permeable to rAAT, and that aerosolized rAAT is capable of gaining access to lung interstitium. No adverse clinical effects were noted. These observations demonstrate that aerosol ***administration*** of rAAT is safe and results in significant augmentation of lung antineutrophil elastase defenses, suggesting this method is a feasible approach to therapy. Because this approach is clinically unproven, further studies will be necessary to establish the long-term clinical efficacy of aerosol therapy in alpha 1AT ***deficiency*** .

L25 ANSWER 28 OF 60 MEDLINE on STN
AN 89321187 MEDLINE
DN PubMed ID: 2787611
TI Anti-neutrophil-elastase defenses of the lower respiratory tract in alpha 1-antitrypsin ***deficiency*** directly augmented with an aerosol of alpha 1-antitrypsin.
AU Hubbard R C; Brantly M L; Sellers S E; Mitchell M E; Crystal R G
CS National Heart, Lung, and Blood Institute, Bethesda, Maryland.
SO Annals of internal medicine, ***(1989 Aug 1)*** Vol. 111, No. 3, pp. 206-12.
Journal code: 0372351. ISSN: 0003-4819.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198908
ED Entered STN: 9 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Aug 1989
AB STUDY OBJECTIVE: To determine if aerosolization of purified human ***plasma*** ***alpha*** ***1*** - ***antitrypsin*** is an effective means for increasing lower respiratory anti-neutrophil-elastase defenses in ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** . DESIGN: Nonrandomized, before-and-after trial with a 7-day treatment period. Companion studies in animals to determine lung epithelial permeability to ***alpha*** ***1*** - ***antitrypsin*** . PATIENTS: Twelve patients with homozygous Z-type ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** and mild to moderate emphysema. INTERVENTIONS: Aerosol ***administration*** of human ***plasma*** ***alpha*** ***1*** - ***antitrypsin*** , 100 mg every 12 hours for 7 days. Single, 100-mg aerosol dose to anesthetized sheep with indwelling thoracic lymph duct catheters for direct assessment of lung permeability. MEASUREMENTS AND MAIN RESULTS: Treatment resulted in increased ***alpha*** ***1*** - ***antitrypsin*** ***levels*** in the lung epithelial lining fluid (0.28 +/- 0.07 microM before therapy to 5.86 +/- 1.03 microM after therapy) and increased anti-neutrophil-elastase capacity (0.78 +/- 0.38 microM before therapy to 4.16 +/- 0.95 microM after therapy). Aerosolized ***alpha*** ***1*** - ***antitrypsin*** diffused across the respiratory epithelium and entered lung interstitial lymph (in sheep) and reached the systemic circulation (in sheep and humans). No side effects were noted. CONCLUSION: Short-term aerosol ***administration*** of human ***plasma*** ***alpha*** ***1*** - ***antitrypsin*** to patients with ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** is safe and feasible, resulting in a return to normal of anti-neutrophil-elastase defenses in the lower respiratory tract. The aerosol approach, therefore, merits serious long-term evaluation as an alternative to other parenteral forms of ***administering***

therapeutic proteins.

L25 ANSWER 29 OF 60 MEDLINE on STN
AN 88300986 MEDLINE
DN PubMed ID: 3261353
TI Biochemical efficacy and safety of monthly augmentation therapy for alpha 1-antitrypsin ***deficiency*** .
AU Hubbard R C; Sellers S; Czerski D; Stephens L; Crystal R G
CS Pulmonary Branch, National Heart, Lung, and Blood Institute, Bethesda, MD 20892.
SO JAMA : the journal of the American Medical Association, ***(1988 Sep*** *** 2)*** Vol. 260, No. 9, pp. 1259-64.
Journal code: 7501160. ISSN: 0098-7484.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198809
ED Entered STN: 8 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 19 Sep 1988
AB The hereditary disorder ***alpha*** ***1*** - ***antitrypsin*** (alpha 1AT) ***deficiency*** results in the development of emphysema due to a diminished anti-neutrophil elastase screen of the lower respiratory tract. Specific therapy for this disorder is available in the form of weekly ***intravenous*** infusions of human ***plasma*** alpha 1AT, which effectively reconstitute the anti-elastase screen of the lung in these individuals. In an attempt to reduce the frequency of therapy we evaluated the ability of monthly infusions of alpha 1AT to provide equivalent lower respiratory tract protection against neutrophil elastase. ***Intravenous*** infusion of 250 mg/kg of alpha 1AT at 28-day intervals to nine individuals with alpha 1AT ***deficiency*** and emphysema was carried out for 12 months. ***Serum*** alpha 1AT ***levels*** exceeded the protective threshold for an average of 25 days after each dose of alpha 1AT was ***administered*** . Furthermore, the postinfusion ***level*** of alpha 1AT in the nadir lung epithelial lining fluid was fivefold greater than the preinfusion ***level*** , and the anti-neutrophil elastase capacity of the nadir epithelial lining fluid also was elevated significantly, nearly threefold above the preinfusion ***level*** . These results indicate that monthly ***administration*** of human alpha 1AT is fully capable of adequately augmenting ***serum*** and lung alpha 1AT ***levels*** and anti-elastase capacity and is therefore a rational alternative to weekly therapy.

L25 ANSWER 30 OF 60 MEDLINE on STN
AN 88250270 MEDLINE
DN PubMed ID: 3289387
TI Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin ***deficiency*** .
AU Hubbard R C; Crystal R G
CS Pulmonary Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland 20892.
SO The American journal of medicine, ***(1988 Jun 24)*** Vol. 84, No. 6A, pp. 52-62. Ref: 45
Journal code: 0267200. ISSN: 0002-9343.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198807

ED Entered STN: 8 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 22 Jul 1988

AB ***Alpha*** - ***1*** - ***antitrypsin*** (A1AT) ***deficiency*** is a genetic disorder characterized by low ***serum*** ***levels*** of A1AT and a high risk for the development of emphysema. A1AT is the principal inhibitor of neutrophil elastase, such that a ***deficiency*** of A1AT results in insufficient anti-elastase protection in the lower respiratory tract, thus allowing neutrophil elastase to destroy alveolar structures. The goal of A1AT augmentation therapy in A1AT ***deficiency*** is to raise lung A1AT ***levels*** and anti-neutrophil elastase capacity to ***levels*** that will provide adequate protection against neutrophil elastase, thereby preventing the lung from further elastase-mediated degradation. Studies with ***intravenous*** ***administration*** of human A1AT (60 mg/kg at weekly intervals) demonstrate that ***serum*** A1AT ***levels*** increased from an average 33 +/- 8 mg/dl pre-infusion to a steady-state trough ***level*** of 117 +/- 4 mg/dl, well above the projected threshold protective ***serum*** ***level*** of A1AT. The infused A1AT diffused into the lung and significantly augmented the epithelial lining fluid A1AT ***levels*** , rising from an average 0.44 +/- 0.16 microM (pre-infusion) to 2.62 +/- 1.29 microM at the nadir ***level*** just prior to the next infusion. Of critical importance is the fact that the A1AT that diffused into the lung was active as an inhibitor or neutrophil elastase, resulting in significant augmentation of epithelial lining fluid anti-neutrophil elastase capacity and normalization of the lung anti-elastase protection. In the over 800 weekly infusions ***administered*** , no significant adverse reactions have occurred. These findings demonstrate that long-term augmentation therapy with weekly infusions of A1AT is a rational, safe, and biochemically effective therapy for A1AT ***deficiency*** .

L25 ANSWER 31 OF 60 MEDLINE on STN
AN 87172923 MEDLINE
DN PubMed ID: 3494198
TI Replacement therapy for alpha 1-antitrypsin ***deficiency*** associated with emphysema.
AU Wewers M D; Casolaro M A; Sellers S E; Swayze S C; McPhaul K M; Wittes J T; Crystal R G
SO The New England journal of medicine, ***(1987 Apr 23)*** Vol. 316, No. 17, pp. 1055-62.
Journal code: 0255562. ISSN: 0028-4793.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198705
ED Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 13 May 1987

AB In patients with ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** , the development of emphysema is believed to be caused by the unchecked action of proteases on lung tissue. We evaluated the feasibility, safety, and biochemical efficacy of intermittent infusions of ***alpha*** ***1*** - ***antitrypsin*** in the treatment of patients with ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** . Twenty-one patients were given 60 mg of active ***plasma*** -derived ***alpha*** ***1*** - ***antitrypsin*** per kilogram of body weight, once a week for up to six months. After a steady state had been reached, the group had trough ***serum*** ***levels*** of ***alpha*** ***1*** - ***antitrypsin*** of 126 +/- 1 mg per deciliter as compared with 30 +/- 1 mg per deciliter before

treatment, and ***serum*** anti-neutrophil elastase capacities of 13.3 +/- 0.1 microM as compared with 5.4 +/- 0.1 microM. The ***alpha*** ***1*** - ***antitrypsin*** ***level*** in the epithelial-lining fluid of the lungs was 0.46 +/- 0.16 microM before treatment, and the anti-neutrophil elastase capacity was 0.81 +/- 0.13 microM. Six days after infusion, ***alpha*** ***1*** - ***antitrypsin*** ***levels*** (1.89 +/- 0.17 microM) and anti-neutrophil elastase capacities (1.65 +/- 0.13 microM) in the lining fluid were significantly increased (P less than 0.0001). Because of the chronicity of the disorder and the lack of sensitive measures of lung destruction, the clinical efficacy of this therapy could not be studied rigorously. No changes in lung function were observed in our patients over six months of treatment. The only important adverse reactions to the 507 infusions were four episodes of self-limited fever. This study demonstrates that infusions of ***alpha*** ***1*** - ***antitrypsin*** derived from ***plasma*** are safe and can reverse the biochemical abnormalities in ***serum*** and lung fluid that characterize this disorder. Together with lifetime avoidance of cigarette smoking, replacement therapy with ***alpha*** ***1*** - ***antitrypsin*** may be a logical approach to long-term medical treatment.

L25 ANSWER 32 OF 60 MEDLINE on STN
AN 87153733 MEDLINE
DN PubMed ID: 3493700
TI Galactosamine-induced ***alpha*** ***1*** - ***antitrypsin*** ***deficiency*** in rats. Alterations in ***plasma*** glycoproteins and ***alpha*** ***1*** - ***antitrypsin*** carbohydrate composition.
AU Bolmer S D; Kleinerman J
NC HL 23595 (NHLBI)
SO The American journal of pathology, ***(1987 Feb)*** Vol. 126, No. 2, pp. 209-19.
Journal code: 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198703
ED Entered STN: 3 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 30 Mar 1987
AB ***Administration*** of D-galactosamine (GalNH2) is known to produce alterations in ***plasma*** glycoprotein ***levels*** , including ***alpha*** ***1*** - ***antitrypsin*** . The authors have studied the effects of GalNH2 on circulating protein bound carbohydrates and on the ***plasma*** concentrations of two alpha 1-antiproteases, transferrin, IgG, and albumin in rats. The alpha 1-antiproteases from GalNH2-treated rats were isolated and their molecular weight, isoelectric point, and carbohydrate composition compared with those of control rat alpha 1-antiproteases. Total ***plasma*** protein, albumin, and transferrin ***levels*** in the GalNH2-treated rats do not differ significantly from those of control rats. ***Plasma*** protein-bound carbohydrate is decreased significantly in the experimental animals, compared with controls: sialic acid decreased 60%, neutral sugars decreased 43%, and amino sugars decreased 38%. The concentrations of ***alpha*** ***1*** - ***antitrypsin*** (AAT) and a higher molecular weight alpha 1-antiprotease designated AP2 are decreased by 79% and 38%, respectively. AAT isolated from the ***plasma*** of GalNH2-treated rats contains 2-3 fewer moles of sialic acid, 3 fewer moles of neutral sugar, and 2 fewer moles of amino sugar per mole of antiprotease than AAT isolated from controls. AP2 from GalNH2-treated rats contains 1 fewer mole each of sialic acid, neutral sugar, and amino

sugar per mole of antiprotease than AP2 from controls. These alterations are similar to those seen in humans with genetically determined alpha 1-antiprotease ***deficiency*** .

L25 ANSWER 33 OF 60 MEDLINE on STN
AN 87126088 MEDLINE
DN PubMed ID: 3492949
TI Evaluation of tamoxifen as a therapy to augment alpha-1-antitrypsin concentrations in Z homozygous alpha-1-antitrypsin- ***deficient*** subjects.
AU Wewers M D; Brantly M L; Casolaro M A; Crystal R G
SO The American review of respiratory disease, ***(1987 Feb)*** Vol. 135, No. 2, pp. 401-2.
Journal code: 0370523. ISSN: 0003-0805.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198703
ED Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 1990
Entered Medline: 11 Mar 1987
AB Tamoxifen, an agent that binds to intracytoplasmic estrogen receptors, was evaluated as a possible means of increasing ***alpha*** - ***1*** - ***antitrypsin*** (alpha 1AT) synthesis and/or secretion and thus alpha 1AT ***serum*** ***levels*** in subjects with the homozygous form of alpha 1AT ***deficiency*** . ***Administration*** of tamoxifen (10 mg twice daily) to 30 Z homozygotes for a 30-day period was not associated with adverse reactions. However, although ***serum*** alpha 1AT ***levels*** increased significantly (p less than 0.03), the increase was minor (average pretreatment ***levels*** , 32 +/- 1 mg/dl; ***levels*** at 30 days of therapy, 35 +/- 1 mg/dl) and far below the "threshold" ***level*** of 80 mg/dl considered "protective" against an increased risk for emphysema. Thus, while the concept that increasing alpha 1AT synthesis and/or secretion is a rational goal for treating the Z homozygous form of alpha 1AT ***deficiency*** , tamoxifen will not be useful in this regard.

L25 ANSWER 34 OF 60 MEDLINE on STN
AN 86212557 MEDLINE
DN PubMed ID: 3085511
TI Isolation and characterization of alpha 1-antitrypsin in PAS-positive hepatic granules from rats with experimental alpha 1-antitrypsin ***deficiency*** .
AU Bolmer S; Kleinerman J
NC HL23595 (NHLBI)
SO The American journal of pathology, ***(1986 May)*** Vol. 123, No. 2, pp. 377-89.
Journal code: 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198606
ED Entered STN: 21 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 9 Jun 1986
AB Chronic galactosamine (GalNH2) ***administration*** in rats decreases ***plasma*** ***alpha*** ***1*** - ***antitrypsin*** (AAT) ***levels*** to 10-50% of control ***levels*** and induces the formation of diastase-resistant, PAS-positive granules, which contain AAT in hepatocytes. This report describes the isolation and purification of

hepatic granule AAT by three different methods: solubilization with guanidine hydrochloride followed by gel filtration on Bio-gel A5M, extraction with methylamine and 2-chloroethanol, and solubilization with sodium dodecyl sulfate (SDS) followed by preparative SDS-polyacrylamide gel electrophoresis. All three methods yield a single protein which precipitates with anti-rat ***plasma*** AAT antibody, and which has an apparent molecular weight of 45,000 daltons, in contrast to the molecular weight of ***plasma*** AAT, 50,000 daltons. Unlike ***plasma*** AAT, granule AAT contains no sialic acid, galactose, or fucose. Moreover, granule AAT contains a reduced amount of N-acetylglucosamine and an increased amount of mannose, compared with ***plasma*** AAT. The carbohydrate content of granule AAT varies with the isolation procedure used. Granule AAT is susceptible to cleavage by endoglucosaminidase H, which indicates the presence of high-mannose type oligosaccharides. Comparison of the molecular weight, carbohydrate composition, isoelectric point, and endoglucosaminidase H sensitivity of granule AAT isolated from rats with GalNH2-induced AAT ***deficiency*** with granule AAT from PiZ humans extends the list of similarities between experimental GalNH2-induced AAT ***deficiency*** in rats by and genetically determined AAT ***deficiency*** in humans.

L25 ANSWER 35 OF 60 MEDLINE on STN
AN 86101532 MEDLINE
DN PubMed ID: 3878676
TI [Neonatal cholestatic icterus simulating atresia of the bile ducts in a patient with alpha-1-antitrypsin ***deficiency***].
Ictericia colestasica neonatal simulando atresia de vias biliares en un paciente con deficit de alfa-1-antitripsina.
AU Sarto Soliva J; Fontana Martinez M; Espigol Requesens D; Alonso Martinez I; Tormo Carnice R; Infante Pina D; Bertran Sangues J M; Moraga Llop F
SO Anales espanoles de pediatria, ***(1985 Oct 15)*** Vol. 23, No. 4, pp. 287-90.
Journal code: 0420463. ISSN: 0302-4342.
CY Spain
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA Spanish
FS Priority Journals
EM 198602
ED Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 7 Feb 1986
AB A 40 days old infant with cholestasis is described. The liver was enlarged at 3 cm below the costal margin. No bile ducts were seen at the liver scan (IDA Tc 99) neither bile was collected after cholecystokinine IV ***administration*** . Fibrosi, bile ducts proliferation, and cholestasis without intracellular PAS positive material were seen at liver biopsy. ***Serum*** ***alpha*** - ***1*** - ***antitrypsin*** ***level*** was 42 mg/100 ml. Follow-up was satisfactory after phenobarbital and cholestiramine treatment. Cholestasis decreased and two weeks later bile excretion was obtained after cholecystokinine ***administration*** . This stress the importance of ***alpha*** - ***1*** - ***antitrypsin*** determination in cholestasis in infancy.

L25 ANSWER 36 OF 60 MEDLINE on STN
AN 85005627 MEDLINE
DN PubMed ID: 6332780
TI [Prevention of complications following abdominal surgical urologic interventions by plasma protein substitutes].
Komplikationsprophylaxe nach abdominalchirurgisch-urologischen Eingriffen durch Plasmaproteinsubstitution.
AU Bauer H W; Mayer P; Schmiedt E

SO Infusionstherapie und klinische Ernahrung, ***(1984 Jun)*** Vol. 11, No. 3, pp. 130-3.
Journal code: 7613112. ISSN: 0378-0791.
CY Switzerland
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA German
FS Priority Journals
EM 198411
ED Entered STN: 20 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 6 Nov 1984
AB A prospective randomised trial in 94 patients undergoing urological abdominal surgery has been carried out to evaluate the effect of postoperatively ***administered*** ***plasma*** proteins. A significant difference between the treatment group and the control group has been found in the incidence of bronchopulmonary complications. This may be due to the substitution of ***Alpha*** - ***1*** ***antitrypsin*** as could be shown by determination of the activity of ***Alpha*** - ***1*** ***antitrypsin*** ***levels*** . A positive trend but no significant differences could be demonstrated for wound healing and the need of antibiotics postoperatively.

L25 ANSWER 37 OF 60 EMBASE
AN 2004528529 EMBASE
TI Intrapleural ***administration*** of a serotype 5 adeno-associated virus coding for . ***alpha*** . ***1*** - ***antitrypsin*** mediates persistent, high lung and ***serum*** ***levels*** of . ***alpha*** . ***1*** - ***antitrypsin*** .
AU De B.; Heguy A.; Leopold P.L.; Wasif N.; Korst R.J.; Hackett N.R.; Crystal R.G.
CS R.G. Crystal, Department of Genetic Medicine, Weill Medical Coll. of Cornell Univ., 515 East 71st Street, New York, NY 10021, United States. geneticmedicine@med.cornell.edu
SO Molecular Therapy, (2004) Vol. 10, No. 6, pp. 1003-1010. .
Refs: 64
ISSN: 1525-0016 CODEN: MTOHCK
PUI S 1525-0016(04)01418-2
CY United States
DT Journal; Article
FS 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
037 Drug Literature Index
039 Pharmacy
LA English
SL English
ED Entered STN: 30 Dec 2004
Last Updated on STN: 30 Dec 2004
AB . ***alpha*** . ***1*** - ***Antitrypsin*** (.alpha.1AT) is a serine proteinase inhibitor that protects the lung from degradation by neutrophil proteases. In .alpha.1AT ***deficiency*** , an autosomal recessive disorder resulting from mutations in the .alpha.1AT (approved symbol SERPINA1) gene, ***serum*** .alpha.1AT ***levels*** of <570 .mu.g/ml are associated with development of emphysema. Adeno-associated virus (AAV) serotype 2 (AAV2) vectors expressing .alpha.1AT ***administered*** intramuscularly or intravenously mediate sustained ***serum*** ***levels*** of .alpha.1AT in experimental animals. Since the lung is only 2% of the body weight, AAV vector delivery to the muscle or liver is inefficient, as most of the .alpha.1AT does not reach

the lung. The present study evaluates AAV2- and AAV5-mediated delivery of human .alpha.1AT (h.alpha.1AT) to C57BL/6 mice using the intrapleural space as a platform for local production of .alpha.1AT. Intrapleural ***administration*** of either an AAV5-h.alpha.1AT or an AAV2-h.alpha.1AT vector achieves higher lung and ***serum*** ***levels*** of .alpha.1AT than intramuscular delivery. AAV5-mediated ***serum*** and lung .alpha.1AT ***levels*** were 10-fold higher than those achieved by AAV2 delivery via either route. The diaphragm, lung, and heart are the major sites of transgene expression following intrapleural ***administration*** of an AAV5 reporter vector. At 40 weeks postadministration, intrapleural ***administration*** of the AAV5-h.alpha.1AT vector mediated ***serum*** .alpha.1AT ***levels*** of 900 .+-. 50 .mu.g/ml, 1.6-fold higher than the accepted therapeutic ***level*** of 570 .mu.g/ml. In the context that the pleura is a safe site for ***administration*** , intrapleural ***administration*** using AAV5 vectors may represent an attractive gene therapy strategy for .alpha.1AT ***deficiency*** in humans.

L25 ANSWER 38 OF 60 EMBASE
AN 2004435262 EMBASE
TI Gene therapy for human .alpha.(1)-antitrypsin ***deficiency*** in an animal model using SV40-Derived vectors.
AU Duan Y.-Y.; Wu J.; Zhu J.-L.; Liu S.-L.; Ozaki I.; Strayer D.S.; Zern M.A.
CS mazern@ucdavis.edu
SO Gastroenterology, (2004) Vol. 127, No. 4, pp. 1222-1232. .
Refs: 40
ISSN: 0016-5085 CODEN: GASTAB
PUI S 0016-5085(04)01387-3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
048 Gastroenterology
LA English
SL English
ED Entered STN: 28 Oct 2004
Last Updated on STN: 28 Oct 2004
AB Background & Aims:In most genetic diseases, the goal of gene therapy is to deliver a particular transgene; however, sometimes a deleterious gene product must be eliminated. Because of the promise of recombinant simian virus 40 (rSV40) vectors, we tested their ability to deliver a transgene and to target a transcript for destruction by direct ***administration*** of the vectors to the liver of an animal model for human . ***alpha*** .(***1***)- ***antitrypsin*** (.alpha.(1)-AT) ***deficiency*** . Methods:Therapy of human .alpha.(1)-AT ***deficiency*** requires stable transduction of resting hepatocytes, both to deliver wild-type .alpha.(1)-AT and to inhibit production of mutant .alpha.(1)-AT. Transgenic mice carrying the mutant human .alpha.(1)-AT PiZ allele were treated through an indwelling portal vein catheter with a simian virus 40 (SV40)-derived vector carrying a ribozyme designed to target the human transcript. Results: Treated transgenic mice showed marked decreases of human .alpha.(1)-AT messenger RNA and the protein in the liver, and ***serum*** ***levels*** of human .alpha.(1)-AT were decreased to 50% .+-. 5% of pretreatment values 3-16 weeks after transduction. Moreover, when normal mice were treated with an SV40-derived vector containing a modified human .alpha.(1)-AT complementary DNA engineered to be resistant to cleavage by the .alpha.(1)-AT ribozyme, they expressed human .alpha.(1)-AT messenger RNA

and protein in their livers and ***serum*** ***levels*** of human .alpha.(1)-AT remained >1 .mu.g/mL for 1 year. Conclusions:These results represent the initial steps toward a novel approach to the gene therapy of .alpha.(1)-AT ***deficiency*** .

L25 ANSWER 39 OF 60 EMBASE

AN 2003397878 EMBASE

TI American Thoracic Society/European Respiratory Society statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin ***deficiency*** .

SO American Journal of Respiratory and Critical Care Medicine, (1 Oct 2003) Vol. 168, No. 7, pp. 818-900. .
ISSN: 1073-449X CODEN: AJCMED

CY United States

DT Journal; General Review

FS 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
037 Drug Literature Index
048 Gastroenterology

LA English

SL English

ED Entered STN: 16 Oct 2003
Last Updated on STN: 16 Oct 2003

AB Goals, Organization of the Project, and Timeline: The goal of the AAT ***Deficiency*** Task Force was to prepare and present for the medical and interested lay communities the reasoned, current views of a large international group of experts regarding the current diagnosis and management of individuals with AAT ***deficiency*** , using a systematic review and the evidence-based approach. The Task Force undertook to evaluate the full clinical and management dimensions of this multisystem illness, including lung, liver, and other organ manifestations. Also, issues relating to the ethical, legal, social, psychological, and economic implications of genetic testing for AAT ***deficiency*** were addressed. A planning group was assembled in the Fall of 1997, when sponsorship and funding by the major sponsors - the American Thoracic Society, the European Respiratory Society, and the Alpha-1 Foundation - was finalized. Additional support from the Alpha-1 Foundation, the American College of Chest Physicians, and the American Association for Respiratory Care allowed the Planning Committee to assemble the full membership of the Task Force and to proceed. As presented in Figure 1, the AAT ***Deficiency*** Task Force consisted of an Executive Committee, three individual Writing Groups comprising international experts, and a Steering Committee (composed of the Executive Committee and the Chairs of each of the three Writing Groups). Preparation of the systematic review was aided by members of the Health Care Technology Assessment Program of the Department of Veterans Affairs, who provided ongoing input and guidance to the project regarding literature searches and evidence-based medicine methods.

Administrative assistance was provided by the American Thoracic Society. The membership of the Task Force was fully constituted by September 1998, at which point Writing Groups began to review literature and to draft documents for subsequent review by the Steering Committee. The Steering Committee conducted a number of conference calls and five face-to-face meetings between Fall 1998 and Fall 2001 to review the evolving documents. Individual Writing Group documents were finalized by Fall 2001 for final editing by the Executive Committee and subsequent submission to the sponsoring organizations. Reviews were received in June 2002 and the revised document was resubmitted in Fall 2002 for final approval. Approval was granted by the American Thoracic Society in December 2002, when an additional review of salient literature led to a

final update of the document. While the Executive Committee has attempted to minimize overlap between the three documents, the Task Force's stated goal of preparing three individual documents, each complete and with its own emphasis, references, and supportive tables and figures, will inevitably lead to some overlap. Finally, in the context that research is ongoing and that current understanding of AAT ***deficiency*** and optimal management is evolving, the Task Force recognizes the need for periodic review and updating of management recommendations. Summary of Main Recommendations Regarding Diagnosis and Management by the ***Alpha*** - ***1*** ***Antitrypsin*** ***Deficiency*** Task Force: Clinical recognition of AAT ***deficiency*** . Available evidence suggests that PI*ZZ AAT ***deficiency*** is frequently underrecognized or misdiagnosed by clinicians. The following features should prompt suspicion by physicians that their patient may be more likely to have AAT ***deficiency*** : .bul. Early-onset emphysema (age of 45 years or less) .bul. Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.) .bul. Emphysema with prominent basilar hyperlucency .bul. Otherwise unexplained liver disease .bul. Necrotizing panniculitis .bul. Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis) .bul. Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis .bul. Bronchiectasis without evident etiology (see below) Notably, in recognizing the discordance of studies concerning whether bronchiectasis is specifically associated with AAT ***deficiency*** , the Task Force recommends discussing AAT testing with individuals who have bronchiectasis without evident etiology, with the understanding that testing could reasonably be accepted or declined. Genetic testing for AAT ***deficiency*** . Recognizing that identifying individuals as having AAT ***deficiency*** can expose them to risks (e.g., of psychologic burden or genetic discrimination), the Task Force recommends that clinicians weigh these risks and discuss them with those for whom testing (by ***serum*** ***level*** or phenotype) is being considered. In evaluating the strength of the Task Force's recommendation to test various individuals for AAT ***deficiency*** , the Task Force recognized four clinical purposes for which testing for AAT ***deficiency*** might be undertaken: (1) diagnostic testing (i.e., to identify symptomatic or otherwise affected individuals), (2) predispositional testing (i.e., to identify asymptomatic individuals who may be at high risk of having AAT ***deficiency***), (3) assessment of carrier status in relation to reproduction, and (4) population screening. Recommendations for genetic testing in specific situations were graded from type A to type D (see Table 1). Each recommendation type was based on the ***level*** of supportive evidence for each issue regarding testing (e.g., the penetrance of AAT ***deficiency*** , population prevalence of AAT ***deficiency*** , clinical impact, accuracy of genetic testing, efficacy of treatment, psychologic and social effects, and economic costs) and the weighing by the Task Force of the issues for or against testing. In the context of this grading scheme, recommendations for the four types of genetic testing are as follows. 1. Diagnostic testing. A type A recommendation for diagnostic testing was made in the following settings: .bul. Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators. (Notably, in populations where the prevalence of AAT ***deficiency*** is known to be much lower than the general North American and Northern European prevalence, a Type B recommendation for diagnostic testing in this setting is offered.) .bul. Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly .bul. Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g., cigarette smoking, occupational exposure) .bul. Adults with necrotizing panniculitis A type B recommendation for diagnostic testing

was made in the following settings: .bul. Adults with bronchiectasis without evident etiology .bul. Adolescents with persistent airflow obstruction .bul..

L25 ANSWER 40 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 2003134280 EMBASE
TI .alpha.(1)-Antitrypsin ***deficiency*** , liver disease and emphysema.
AU Parfrey H.; Mahadeva R.; Lomas D.A.
CS H. Parfrey, Department of Medicine, University of Cambridge, Cambridge Inst. for Medical Research, Hills Road, Cambridge CB2 2XY, United Kingdom. hp226@cam.ac.uk
SO International Journal of Biochemistry and Cell Biology, (1 Jul 2003) Vol. 35, No. 7, pp. 1009-1014. .
Refs: 16
ISSN: 1357-2725 CODEN: IJBBFU
PUI S 1357-2725(02)00250-9
CY United Kingdom
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
ED Entered STN: 10 Apr 2003
Last Updated on STN: 10 Apr 2003
AB . ***alpha*** .(***1***)- ***Antitrypsin*** is a member of the serine proteinase inhibitor (serpin) superfamily and a potent inhibitor of neutrophil elastase. The most important ***deficiency*** variant of . ***alpha*** .(***1***)- ***antitrypsin*** arises from the Z mutation (Glu342Lys). This mutation perturbs the protein's tertiary structure to promote a precise, sequential intermolecular linkage that results in polymer formation. These polymers accumulate within the endoplasmic reticulum of the hepatocyte forming inclusion bodies that are associated with neonatal hepatitis, juvenile cirrhosis and adult hepatocellular carcinoma. The resultant secretory defect leads to ***plasma*** ***deficiency*** of . ***alpha*** .(***1***)- ***antitrypsin*** . This exposes lung tissue to uncontrolled proteolytic attack from neutrophil elastase, culminating in alveolar destruction. Thus, the Z . ***alpha*** .(***1***)- ***antitrypsin*** homozygote is predisposed to developing early onset basal, panacinar emphysema. In this review, we summarise the current understanding of the pathobiology of . ***alpha*** .(***1***)- ***antitrypsin*** ***deficiency*** and the associated liver cirrhosis and emphysema. We show how this knowledge has led to the development of novel therapeutic approaches to treat this condition. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L25 ANSWER 41 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 2002249245 EMBASE
TI Biochemical efficacy and safety of a new pooled human ***plasma*** . ***alpha*** .(***1***)- ***antitrypsin*** , ***Respitin*** .
AU Stoller J.K.; Rouhani F.; Brantly M.; Shahin S.; Dweik R.A.; Stocks J.M.; Clausen J.; Campbell E.; Norton F.
CS Dr. J.K. Stoller, Department of Pulmonary Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, United States. stollej@ccf.org
SO Chest, (2002) Vol. 122, No. 1, pp. 66-74. .
Refs: 20

ISSN: 0012-3692 CODEN: CHETBF
CY United States
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 25 Jul 2002
Last Updated on STN: 25 Jul 2002
AB Background: Augmentation therapy with pooled human ***plasma*** -derived . ***alpha*** .(***1***)- ***antitrypsin*** (AAT) has been shown to have biochemical efficacy in restoring ***serum*** AAT ***levels*** above the protective threshold. Also, clinical efficacy has been suggested. Objective: To evaluate the bioequivalence of a new solvent detergent-treated preparation of pooled human ***plasma*** -derived AAT (proposed name ***Respitin*** ; Alpha Therapeutic Corporation; Los Angeles, CA) to the commercially available preparation (***Prolastin*** ; Bayer Corporation; West Haven, CT), we conducted a randomized controlled trial. Methods: Eligible subjects were adults (> 18 years of age) who had never smoked or were ex-smokers, had severe ***deficiency*** of AAT, and had fixed airflow obstruction (ie, postbroncholdilator FEV1 of 30 to 80% of predicted values and/or diffusing capacity of the lung for carbon monoxide [DLCO] of < 70% of predicted values with evidence of emphysema on a CT scan). Of the 28 subjects recruited, 26 completed the 12-week comparison. Participants were randomized to receive ***Respitin*** (60 mg/kg once weekly; 14 subjects) or ***Prolastin*** (60 mg/kg once weekly; 14 subjects), and recipients of ***Prolastin*** then crossed over to receive ***Respitin*** thereafter for the 24-week duration of the study. Results: The primary efficacy criteria were satisfied for equivalence to comparator (ie, the ratio of mean trough ***serum*** ***levels*** for ***Respitin*** / ***Prolastin*** at weeks 8 to 11 exceeded the efficacy criterion [0.905; p 3 0.0206] as did the slope of the mean trough ***level*** over weeks 11 to 23 [30.003 3mol per week]). In ***Respitin*** recipients, the trough ***serum*** antineutrophil elastase capacity at week 7 and at weeks 8 to 11 was also equivalent to the comparator, as was the rise in AAT ***levels*** in epithelial lining fluid from baseline to week 7. The ***levels*** of urinary elastin degradation products showed little appreciable change for > 24 weeks, and no difference between compared groups was shown through week 12. Adverse events were similarly infrequent in compared groups. Finally, neither spirometry measurements nor DLCO showed a significant change through 24 weeks. Conclusions: We conclude that this new solvent detergent-treated pooled human ***plasma*** -derived AAT (***Respitin***) demonstrates biochemical equivalence to ***Prolastin*** and that this new drug is well-tolerated.

L25 ANSWER 42 OF 60 EMBASE
AN 2001317339 EMBASE
TI Stable therapeutic ***serum*** ***levels*** of human ***alpha*** - ***1*** ***antitrypsin*** (AAT) after portal vein injection of recombinant adeno-associated virus (rAAV) vectors.
AU Song S.; Embury J.; Laipis P.J.; Berns K.I.; Crawford J.M.; Flotte T.R.
CS T.R. Flotte, Univ. of Florida College of Medicine, Gene Therapy Center, Department of Pediatrics, 1600 SW Archer Road, Gainesville, FL 32610-0266, United States
SO Gene Therapy, (2001) Vol. 8, No. 17, pp. 1299-1306. .
Refs: 33
ISSN: 0969-7128 CODEN: GETHEC

CY United Kingdom
DT Journal; Article
FS 004 Microbiology
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 27 Sep 2001
Last Updated on STN: 27 Sep 2001
AB Previous work from our group showed that recombinant adeno-associated virus (rAAV) vectors mediated long-term secretion of therapeutic ***serum*** ***levels*** of human ***alpha*** - ***1*** ***antitrypsin*** (hAAT) after a single injection in murine muscle. We hypothesized that hepatocyte transduction could be even more efficient, since these cells represent the natural site of AAT production and secretion. To test this hypothesis, rAAV vectors containing the hAAT cDNA driven by either the human elongation factor 1 alpha promoter, the human cytomegalovirus immediate-early promoter (CMV), or the CMV-chicken beta actin hybrid (CB) promoter were injected into the portal or tail veins of adult C57BI/6 mice. Potentially therapeutic ***serum*** ***levels*** of hAAT (600 .mu.g/ml) were achieved after portal vein injection of doses of 4 x 10(9) infectious units (IU), a 10-fold lower dose than that required for similar ***levels*** of expression via the i.m. route. ***Serum*** ***levels*** greater than 1 mg/ml were achieved at doses of 3 x 10(10) IU. Southern blotting of liver DNA revealed the presence of circular episomal vector genomes. Immunostaining showed that transgene expression was scattered throughout the liver parenchyma. Similar results were obtained with a rAAV-CB-green fluorescent protein (GFP) vector. There was no evidence of hepatic toxicity. These data indicate that liver-directed rAAV-based gene therapy is effective in the murine model, and hence might be feasible for treatment of human AAT ***deficiency*** .

L25 ANSWER 43 OF 60 EMBASE
AN 2000098689 EMBASE
TI Therapy for .alpha.1-antitrypsin ***deficiency*** : Pharmacology and clinical recommendations.
AU Minai O.A.; Stoller J.K.
CS Dr. J.K. Stoller, Dept. of Pulmonary/Crit. Care Med., Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. stollej@ccf.org
SO BioDrugs, (2000) Vol. 13, No. 2, pp. 135-147. .
Refs: 37
ISSN: 1173-8804 CODEN: BIDRF4
CY New Zealand
DT Journal; General Review
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English
ED Entered STN: 30 Mar 2000
Last Updated on STN: 30 Mar 2000
AB . ***alpha*** . ***1*** - ***Antitrypsin*** (A1AT) ***deficiency*** is inherited as an autosomal codominant disorder characterised by reduced ***levels*** of A1AT in the ***serum*** . Low ***levels*** of A1AT in blood perfusing the lung cause low ***levels*** in the lung interstitium, making it susceptible to proteolytic damage from resident neutrophil elastase. A 'protective threshold' ***serum*** A1AT ***level*** of 11 .mu.mol/L has been identified by epidemiological studies as a minimum value below which there

is an increased risk of emphysema. ***Intravenous*** augmentation therapy for patients with severe ***deficiency*** of A1AT has been shown to have biochemical efficacy. Although the clinical efficacy of ***intravenous*** augmentation therapy has not been demonstrated in a randomised clinical trial, available studies suggest that augmentation therapy is associated with a slowed rate of decline of lung function and enhanced survival. The criteria for patient selection include: age > 18 years, ***serum*** A1AT ***level*** .ltoreq.11 .mu.mol/L, a high-risk phenotype (usually PI*ZZ), and documented fixed airflow obstruction (consistent with chronic obstructive pulmonary disease). Although ***intravenous*** augmentation is currently the only form of specific therapy approved in the US, active research in the fields of aerosol and gene therapy promise to offer new treatment prospects. In this article, we review the available literature on A1AT augmentation therapy and discuss our recommendations.

L25 ANSWER 44 OF 60 EMBASE

AN 1999282363 EMBASE

TI New developments in alpha 1-antitrypsin ***deficiency*** .

AU Aboussouan L.S.; Stoller J.K.

CS Dr. L.S. Aboussouan, Wayne State Univ. School of Medicine, Div. of Pulmonary/Critical Care Med., Harper Hospital, Detroit, MI 48201, United States

SO Seminars in Respiratory and Critical Care Medicine, (1999) Vol. 20, No. 4, pp. 301-310. .
Refs: 71
ISSN: 1069-3424 CODEN: SRCCEX

CY United States

DT Journal; General Review

FS 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index

LA English

SL English

ED Entered STN: 26 Aug 1999
Last Updated on STN: 26 Aug 1999

AB ***Alpha*** ***1*** - ***antitrypsin*** ***deficiency*** is an autosomal codominant condition associated with the development of premature emphysema, chronic liver disease, diseases of arterial vascular tissue such as aneurysm formation, and possibly vasculitis. Whereas unchecked proteolytic activity of neutrophil elastase is the likely etiology of premature emphysema and diseases of arterial vascular tissue, chronic liver disease has only recently been proposed to be due to loop-sheet polymerization of the most common ***deficiency*** variant of the ***alpha*** ***1*** - ***antitrypsin*** molecule, the PI*ZZ mutant. Recent evidence suggests that this disorder is underrecognized by health care providers with only 4% of the estimated 60,000 to 100,000 Americans having been identified. ***Intravenous*** augmentation therapy with purified pooled ***plasma*** derived ***alpha*** ***1*** - ***antitrypsin*** has been shown to have biochemical efficacy in raising ***serum*** and alveolar lining fluid ***levels*** to above protective thresholds. Although uncontrolled studies suggest additional clinical efficacy, no randomized clinical trials of ***intravenous*** augmentation therapy have been reported to date. The use of gene therapy is currently limited by difficulties in obtaining sustained and therapeutic ***levels*** of ***alpha*** ***1*** - ***antitrypsin*** expression. ***Alpha*** ***1*** - ***antitrypsin*** ***deficiency*** accounts for 11% of all lung transplants performed, with post-transplantation survival rates of 45% at 5 years matching those of lung transplantation for chronic obstructive pulmonary disease in general. These recent advances raise further

challenges such as the role of population screening, the prospects of newer therapies such as inhaled augmentation and gene therapy, and the feasibility of randomized placebo-controlled clinical trials.

L25 ANSWER 45 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 1999242504 EMBASE
TI The acute-phase protein response to human immunodeficiency virus infection in human subjects.
AU Jahoor F.; Gazzard B.; Phillips G.; Sharpstone D.; Delrosario M.; Frazer M.E.; Heird W.; Smith R.; Jackson A.
CS F. Jahoor, USDA/ARS Children's Nutri. Res. Ctr., Dept. of Pediatrics, Baylor College of Medicine, 1100 Bates St., Houston, TX 77030-2600, United States. fj@ahoor@bcm.tmc.edu
SO American Journal of Physiology - Endocrinology and Metabolism, (1999) Vol. 276, No. 6 39-6, pp. E1092-E1098. .
Refs: 26
ISSN: 0193-1849 CODEN: AJPMD
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
SL English
ED Entered STN: 2 Aug 1999
Last Updated on STN: 2 Aug 1999
AB Although several studies have shown that asymptomatic human immunodeficiency virus infection elicits an increase in whole body protein turnover, it is not known whether this increased protein turnover includes changes in the kinetics of acute-phase proteins (APPs). To answer this question, we measured 1) the ***plasma*** concentrations of four positive (C- reactive protein, . ***alpha*** . ***1*** - ***antitrypsin*** , haptoglobin, and fibrinogen) and four negative APPs [albumin, high-density lipoprotein (HDL)-apolipoprotein (apo) A1, transthyretin, and retinol-binding protein] and 2) the fractional (FSR) and absolute (ASRs) synthesis rates of three positive and three negative APPs using a constant ***intravenous*** infusion of [2H5]phenylalanine in five subjects with symptom-free acquired immunodeficiency syndrome (AIDS) and five noninfected control subjects. Compared with the values of the controls, the ***plasma*** concentrations, FSRs, and ASRs of most positive APPs were higher in the AIDS group. The negative APPs had faster FSRs in the AIDS group, there was no difference between the ASRs of the two groups, and only HDL-apoA1 had a lower ***plasma*** concentration. These results suggest that symptom-free AIDS elicits an APP response that is different from bacterial infections, as the higher concentrations and faster rates of synthesis of the positive APPs are not accompanied by lower concentrations and slower rates of synthesis of most of the negative APPs.

L25 ANSWER 46 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 1999079288 EMBASE
TI [Alpha-1-protease inhibitor ***deficiency*** and pulmonary emphysema as viewed by pulmonary specialists in private praxis].
ALPHA-1-PROTEINASENINHIBITOR-MANGEL UND LUNGENEMPHYSEM AUS DER SICHT DES NIEDERGELASSENEN PNEUMOLOGEN.
AU Wencker M.; Konietzko N.
CS Dr. M. Wencker, Kuhlmannsfeld 53, D-45355 Essen, Germany
SO Atemwegs- und Lungenkrankheiten, (1999) Vol. 25, No. 2, pp. 89-95. .
Refs: 25
ISSN: 0341-3055 CODEN: ATLUDF
CY Germany

DT Journal; Article
FS 006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA German
SL English; German
ED Entered STN: 26 Mar 1999
Last Updated on STN: 26 Mar 1999
AB In a multicenter mail survey 210 pneumologists or internal medicine physicians specialized on pneumology in private praxis were asked about their experience with pulmonary emphysema, particularly referring to alpha-1- protease inhibitor (.alpha.-Pi) ***deficiency*** . The mean percentage of patients with pulmonary emphysema seen by pulmonary specialists in private praxis was 17%, a total of 5% of the patients had clinically relevant emphysema. The main reason for referral to the pulmonary specialist was the worsening of the patient despite therapy. Additionally to a physical examination, pulmonary function tests, blood gas analysis, and chest X-ray, 67% of the physicians included the determination of ***serum*** .alpha.1-Pi ***levels*** as a routine diagnostic method in suspected pulmonary emphysema. Approximately 2.7% or 3 patients with emphysema suffered from severe .alpha.1-Pi ***deficiency*** . 51% of the respiratory specialists had experience with ***intravenous*** augmentation therapy with human .alpha.1-Pi (***Prolastin*** HS) and the vast majority applied 60 mg/kg body weight once weekly. 56% of the pulmonary specialists reported a stabilization of pulmonary function due to augmentation therapy and 31% thought it was too early to evaluate the effect. The therapeutic intervention in patients with severe .alpha.1-Pi ***deficiency*** includes strict non-smoking, vaccination against influenza and pneumococci, vigorous treatment of pulmonary infections and avoiding harmful smokes and fumes.

L25 ANSWER 47 OF 60 EMBASE
AN 97317992 EMBASE
DN 1997317992
TI Continuous mannose infusion in carbohydrate- ***deficient*** glycoprotein syndrome type I.
AU Mayatepek E.; Schroder M.; Kohlmuller D.; Bieger W.P.; Nutzenadel W.
CS E. Mayatepek, Division of Metabolic Diseases, University Children's Hospital, Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany
SO Acta Paediatrica, International Journal of Paediatrics, (1997) Vol. 86, No. 10, pp. 1138-1140. .
Refs: 11
ISSN: 0803-5253 CODEN: APAEEL
CY Norway
DT Journal; Article
FS 007 Pediatrics and Pediatric Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 30 Oct 1997
Last Updated on STN: 30 Oct 1997
AB The effects on isoelectrofocusing patterns of ***serum*** glycoproteins were studied in a patient with CDG syndrome type I and phosphomannomutase ***deficiency*** during 3 weeks of continuous ***intravenous*** mannose infusion. Doses of 5.7 g/kg/day led to stable ***serum*** mannose ***levels*** up to 2.0 mmol/l and were well tolerated without signs of liver or renal toxicity. While most of the pathological glycoprotein patterns, including . ***alpha*** . ***1*** - ***antitrypsin*** , typical for CDG syndrome type I remained unchanged, mannose infusion led to a unique change of the

isoelectrofocusing pattern of ***serum*** sialotransferrins with appearance of two extra bands after 3 weeks of treatment.

L25 ANSWER 48 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 97295012 EMBASE
DN 1997295012
TI Pharmacokinetic study of .alpha.1-antitrypsin infusion in .alpha.1-antitrypsin ***deficiency*** .
AU Barker A.F.; Iwata-Morgan I.; Oveson L.; Roussel R.
CS Dr. A.F. Barker, Dept. of Med., Oregon Health Sciences University, Portland, CA, United States
SO Chest, (1997) Vol. 112, No. 3, pp. 607-613. .
Refs: 13
ISSN: 0012-3692 CODEN: CHETBF
CY United States
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
ED Entered STN: 16 Oct 1997
Last Updated on STN: 16 Oct 1997
AB Objectives: To ascertain how long 120 mg/kg alpha1-antitrypsin concentrate (.alpha.1-AT-C), ***administered*** IV every 2 weeks, can maintain . ***alpha*** . ***1*** - ***antitrypsin*** (.alpha.1-AT) ***serum*** ***levels*** above 70 to 80 mg/dL. Secondary objectives were to summarize the nature, severity, and relationship of a ***plasma*** -derived .alpha.1-AT-C infusion to any side effects. Methods: This was an open-label uncontrolled pharmacokinetic study. .alpha.1-AT-C was ***administered*** IV every 2 weeks for 10 infusions in 23 patients with PIZ .alpha.1-AT ***deficiency*** . ***Serum*** .alpha.1-AT ***levels*** and neutralizing elastase activity were measured preinfusion, postinfusion, and at nadir. During two infusion periods, daily ***serum*** .alpha.1-AT and neutralizing elastase activities were measured on the seventh to 14th days. Five patients received BAL assays for .alpha.1-AT and neutralizing elastase activity. Adverse events were recorded in a patient diary and by a nurse at each infusion visit. Results: The 120-mg/kg dose of .alpha.1-AT-C could not maintain nadir ***serum*** protective ***levels*** above 70 or 80 mg/dL for the entire 14-day dosing interval in most patients. None of the patients had .alpha.1-AT ***levels*** above 80 mg/dL for all 14 days. The ***serum*** .alpha.1-AT and neutralizing elastase ***levels*** correlated suggesting functional activity. The BAL .alpha.1-AT and neutralizing elastase activities were low and did not correlate with ***serum*** ***levels*** . Conclusion: .alpha.1-AT-C at 120 mg/kg ***administered*** every 2 weeks did not maintain nadir ***serum*** .alpha.1-AT ***levels*** above 70 to 80 mg/dL for a 14- day dosing interval. Higher doses every 2 weeks or decreased interval between infusions may be required.

L25 ANSWER 49 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 90393715 EMBASE
DN 1990393715
TI Molecular analysis of the heterogeneity among the P-family of alpha-1-antitrypsin alleles.
AU Holmes M.D.; Brantly M.L.; Crystal R.G.
CS Building 10, National Inst. of Health,Bethesda, MD 20892, United States
SO American Review of Respiratory Disease, (1990) Vol. 142, No. 5, pp.

1185-1192. .
ISSN: 0003-0805 CODEN: ARDSBL
CY United States
DT Journal; Article
FS 006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 13 Dec 1991
Last Updated on STN: 13 Dec 1991
AB The rare P-family of . ***alpha*** . ***1*** - ***antitrypsin*** (.alpha.1AT) variants is defined by the position of migration of the .alpha.1AT protein on isoelectric focusing of ***serum*** (IEF) between the common M and S variants. To begin to examine the molecular heterogeneity among the P-type alleles, two unrelated subjects and their families identified by IEF to be carrying a P allele were analyzed. The first, P(lowell), is a ***deficiency*** allele associated with reduced ***serum*** .alpha.1AT ***levels*** , and the second, P(saint albans), is associated with normal ***serum*** ***levels*** . DNA sequence analysis of P(lowell), the more anodal of the two variants on IEF analysis, showed that it differed from the normal M1(Val213) allele by a single base and amino acid substitution Asp256 GAT .fwdarw. Val GTT. In contrast, P(saint albans), a slightly more cathodally positioned variant on IEF analysis, differed from the coding exons of the normal M1(Val213) allele by two mutations, Asp341 GAC .fwdarw. Asn AAC, and a silent substitution in the same codon as the P(lowell) variant, Asp256 GAT .fwdarw. Asp GAC. Evaluation of P(lowell) mRNA transcripts by Northern and cytoblot analyses demonstrated they were of normal size and amount, and P(lowell) mRNA transcripts could be translated normally in vitro. Retroviral insertion of the P(lowell) cDNA into the genome of 3T3 fibroblasts demonstrated that it directed the synthesis of .alpha.1AT, but at ***levels*** 24% that of the P(saint albans) cDNA or the normal M1 (Val213) cDNA, with a pattern of biosynthesis consistent with the concept that the P(lowell) .alpha.1AT ***deficiency*** state results from intracellular degradation of the newly synthesized P(lowell) protein. In the context that the ***serum*** .alpha.1AT ***deficiency*** associated with other .alpha.1AT ***deficiency*** mutations resulting from intracellular degradation of .alpha.1AT can be overcome by ***administering*** estrogenlike drugs, ***administration*** of tamoxifen to a subject with the P(lowell)Z phenotype resulted in .alpha.1AT ***serum*** ***levels*** rising 48% over a 5-month period, from below the threshold for protection from emphysema (11 .mu.M) to above that threshold.

L25 ANSWER 50 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 77026939 EMBASE
DN 1977026939
TI Protease inhibitors in plasma of patients with chronic urticaria.
AU Doeglas H.M.G.; Bleumink E.
CS Dept. Dermatol., State Univ., Groningen, Netherlands
SO Archives of Dermatology, (1975) Vol. 111, No. 8, pp. 979-985. .
CODEN: ARDEAC
DT Journal
FS 013 Dermatology and Venereology
025 Hematology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LA English
AB The hypothesis that ***deficiencies*** of ***plasma*** protease

inhibitors might play a role in the pathogenesis of chronic urticaria was evaluated. ***Plasma*** ***levels*** were measured in patients with urticaria and a matched control group for . ***alpha*** . ***1*** ***antitrypsin*** , .alpha.2 macroglobulin, total trypsin inhibiting capacity, kallikrein inhibiting capacity, and the complement factors C1 esterase inhibitor, C3, and C4. A total of 92 patients with chronic urticaria of more than 3 mth duration was studied. Patients with acquired cold urticaria had significantly decreased ***levels*** of . ***alpha*** . ***1*** ***antitrypsin*** and total antitrypsin activity. In patients with acquired angioneurotic edema, . ***alpha*** . ***1*** ***antitrypsin*** ***levels*** and antichymotrypsin activities were lowered, with less significant decreases in antitrypsin and antikallikrein activities. ***Levels*** of C1 esterase inhibitor, C3, and C4 were normal in all groups. There was no correlation between the increased sensitivity to intracutaneously ***administered*** kallikrein injection and ***deficiencies*** of protease inhibitors.

L25 ANSWER 51 OF 60 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
AN 74159904 EMBASE
DN 1974159904
TI Emphysema associated with talcum granulomatosis in a drug addict.
AU Vevaina J.R.; Civantos F.; Viamonte Jr M.; Avery W.G.
CS Div. Pulm. Dis., Dept. Int. Med., Lab. Med. Radiol., Mt. Sinai Hosp., Miami, Fla. 33140, United States
SO Southern Medical Journal, (1974) Vol. 67, No. 1, pp. 113-116. .
CODEN: SMJOAV
DT Journal
FS 037 Drug Literature Index
015 Chest Diseases, Thoracic Surgery and Tuberculosis
006 Internal Medicine
LA English
AB A 42 yr old narcotic addict with a 15 yr history of ***intravenous*** injection of a water solution of methadone tablets developed signs and symptoms of severe pulmonary emphysema. Wheezing usually occurred after each injection of crushed methadone tablets. ***Serum*** ***alpha*** ***1*** ***antitrypsin*** ***levels*** were normal. Pulmonary angiography revealed evidence of pulmonary emphysema and embolic disease. Pulmonary function studies showed changes consistent with severe obstructive lung disease. The marked diminution of diffusing capacity suggested massive reduction of the pulmonary capillary bed. Lung biopsy showed panacinar emphysema and multiple talc granulomas arising in the alveolar septa.

L25 ANSWER 52 OF 60 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2006:79601 BIOSIS
DN PREV200600086342
TI Lack of effect of 4-phenylbutyrate on ***levels*** of alpha-1-antitrypsin in patients with alpha 1AT ***deficiency*** .
AU Teckman, Jeffrey
SO Gastroenterology, (***APR 2004***) Vol. 126, No. 4, Suppl. 2, pp. A666.
Meeting Info.: Digestive Disease Week/105th Annual Meeting of the American-Gastroenterological-Association. New Orleans, LA, USA. May 16 -20, 2004. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 25 Jan 2006
Last Updated on STN: 25 Jan 2006

AB The function of the hepatic secretary protein, ***alpha*** - ***1*** - ***antitrypsin*** (alpha 1AT) is to protect host tissues from damage by inhibiting neutrophil proteases. In homozygous, ZZ alpha 1AT ***deficiency*** , a mutant gene encodes a mutant protein, which acquires as abnormal conformation during biosynthesis and accumulates within hepatocytes rather than being secreted. ZZ individuals have a markedly increased risk of developing pulmonary emphysema as a result of the reduced ***level*** of circulating anti-protease activity. Some ZZ homozygotes also develop liver injury and hepatocellular carcinoma caused by accumulation of mutant alpha 1ATZ protein within hepatocytes. alpha 1AT protein replacement therapy is available to treat alpha 1AT ***deficiency*** emphysema, although this product has no proven clinical efficacy. There is no specific therapy for alpha 1AT ***deficiency*** liver disease. The drug 4-phenylbuterate (4-PBA) has been shown to increase the secretion of mutant alpha 1ATZ protein in cell culture, and to mediate a two-fold increase in circulating alpha 1AT ***levels*** when given enterally to a mouse model of alpha 1AT ***deficiency*** . Its similar increase in ***serum*** ***levels*** were achieved in humans it might be sufficient to prevent the development of emphysema, and could possibly reduce the hepatotoxic accumulation of alpha 1ATZ protein. We, therefore, hypothesized that 4-PBA might be therapeutic in humans lot both the liver and lung disease associated with alpha 1AT ***deficiency*** by mediating increased secretion of alpha 1ATZ protein from the liver. In a preliminary, open label study we enrolled 10 alpha 1AT ***deficient*** patients to evaluated the effect of two weeks of oral 4-PBA on changes in a I AT blood ***levels*** , and to document the occurrence of side effects in the setting of alpha 1AT ***deficiency*** liver disease. The maximum approved dose was used, and pill counts and ***serum*** drug ***levels*** suggested that study compliance was high. However, the results showed no significant increases in the patient's alpha 1AT blood ***levels*** associated with 4-PBA ***administration*** (t-test p=0.45, N.S.). Symptomatic and metabolic side effects were burdensome, and were more pronounced in patients with signs of portal hypertension. In conclusion, 4-PBA is ineffective at increasing alpha 1AT blood ***levels*** in humans and is unlikely to be an effective treatment for alpha 1AT ***deficiency*** emphysema There is also no evidence of a beneficial effect on the liver in this preliminary trial.

L25 ANSWER 53 OF 60 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2004:123302 BIOSIS
DN PREV200400116606
TI NSAIDS increase a-1-antitrypsin protein synthesis and increase liver injury in a model of a1AT ***deficiency*** .
AU Rudnick, David [Reprint Author]; Teckman, Jeffrey [Reprint Author]
CS Washington University School of Medicine, Saint Louis, MO, USA
SO Hepatology, (***October 2003***) Vol. 38, No. 4 Suppl. 1, pp. 231A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB Homozygous (ZZ) ***alpha*** - ***1*** - ***antitrypsin*** (alpha1AT) ***deficiency*** is an important cause of liver disease in children, and can also cause chronic liver disease and hepatocellular carcinoma in adults. The alpha1AT mutant Z gene encodes a mutant protein

which accumulates in the endoplasmic reticulum of hepatocytes rather than being secreted appropriately into the ***serum*** . Liver injury is caused by this accumulation of alpha1AT mutant Z protein within hepatocytes, which then triggers downstream intracellular injury pathways. However, the development of clinical liver disease among ZZ homozygotes is highly variable, suggesting that there is a significant influence of other genetic or environmental factors which contribute to liver injury. In this study, we tested the hypothesis that non-steroidal anti-inflammatory drugs (NSAIDS) could be a co-factor in the development of liver injury in alpha1AT ***deficiency*** using the PiZ mouse, a model transgenic for the human alpha1AT mutant Z gene in which gene expression is regulated by the human alpha1AT promoter sequences. The results showed that indomethacin ***administered*** in typically non-toxic murine doses to PiZ mice was associated with increased alpha1AT gene transcription as determined by RT-PCR analysis of alpha1AT mRNA ***levels*** , and increased hepatic alpha1AT mutant Z protein content, as shown by increased globular accumulations of alpha1AT in histopathologic sections and by quantitative immunoblot analysis of liver lysates for human alpha1AT protein. Furthermore, indomethacin treatment in PiZ mice was associated with increased hepatic injury and increased mortality compared to that seen in vehicle-treated PiZ mice and indomethacin treated wildtype mice. Evidence of hepatic injury included focal hepatocellular necrosis, hepatic caspase 9 activation, and increased hepatocellular proliferation as a compensatory response to increased cell death. In conclusion, these data suggest that environmental factors, such as exogenous medication ***administration*** can significantly potentiate the liver injury associated with alpha1AT mutant Z hepatic accumulation, and that NSAIDS may be especially injurious to ZZ patients, possibly by mediating increased alpha1AT synthesis.

L25 ANSWER 54 OF 60 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 1998:271741 SCISEARCH
GA The Genuine Article (R) Number: ZC681
TI Long-term treatment of alpha(1)-antitrypsin ***deficiency*** -related pulmonary emphysema with human alpha(1)-antitrypsin
AU Wencker M (Reprint); Banik N; Buhl R; Seidel R; Konietzko N
CS Tuschener Weg 40, D-45239 Essen, Germany (Reprint); Univ Hosp, Ruhrlandklin, Essen, Germany; Bayer Vital GmbH Co KG, Leverkusen, Germany; Univ Frankfurt, Dept Pulm, D-6000 Frankfurt, Germany
Corporate Author: WATL-alpha1-AT-study grp
CYA Germany
SO EUROPEAN RESPIRATORY JOURNAL, (***FEB 1998***) Vol. 11, No. 2, pp. 428-433.
ISSN: 0903-1936.
PB EUROPEAN RESPIRATORY SOC JOURNALS LTD, 146 WEST ST, STE 2.4, HUTTONS BLDG, SHEFFIELD S1 4ES, ENGLAND.
DT Article; Journal
LA English
REC Reference Count: 29
ED Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB ***alpha*** (***1***)- ***antitrypsin*** (alpha(1)-AT) ***deficiency*** is a genetic disorder characterized by low ***serum*** ***levels*** of alpha(1)-AT and a high risk of pulmonary emphysema at a young age. The resulting surplus of proteases, mainly of neutrophil elastase, can be balanced by i.v. augmentation with alpha(1)-AT. However, it is not clear if affected patients benefit from long-term augmentation therapy and no long-term safety data are available.
We examined 443 patients with severe alpha(1)-AT ***deficiency*** and pulmonary emphysema receiving weekly i.v. infusions of 60 mg.kg body

weight(-1) alpha(1)-AT in addition to their regular medication, The progression of the disease was assessed by repeated lung function measurements, particularly the decline in forced expiratory volume in one second (Delta FEV1),

Four hundred and forty three patients with alpha(1)-AT ***deficiency*** tolerated augmentation therapy well with fen adverse reactions, The Delta FEV1 in 287 patients with available follow-up data was 57.1+/-31.1 mL.yr(-1). Stratified for baseline FEV1, the decline was 35.6+/-21.3 mt in the 108 patients with an initial FEV1 <30% and 64.0+/-26.4 mt in the 164 with FEV1 30-65% of predicted normal (p=0.0008). The remaining 15 patients had an initial FEV1 >65% pred.

Long-term treatment with i.v. alpha(1)-antitrypsin in patients with severe alpha(1)-antitrypsin ***deficiency*** is feasible and safe, The decline in forced expiratory volume in one second is related to the initial forced expiratory volume in one second as in alpha(1)-antitrypsin ***deficient*** patients not receiving augmentation therapy.

L25 ANSWER 55 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 2000:30118522 BIOTECHNO
TI Chemical chaperones mediate increased secretion of mutant . ***alpha*** . ***1*** - ***antitrypsin*** (.alpha.1-AT) Z: A potential pharmacological strategy for prevention of liver injury and emphysema in .alpha.1-AT ***deficiency***
AU Burrows J.A.J.; Willis L.K.; Perlmutter D.H.
CS D.H. Perlmutter, Department of Pediatrics, Washington Univ. School of Medicine, Div. of Gastroenterology and Nutri., St. Louis, MO 63110, United States.
E-mail: perlmutter@kids.wustl.edu
SO Proceedings of the National Academy of Sciences of the United States of America, ***(15 FEB 2000)*** , 97/4 (1796-1801), 27 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DT Journal; Article
CY United States
LA English
SL English
AB In .alpha.1-AT ***deficiency*** , a misfolded but functionally active mutant .alpha.1-ATZ (.alpha.1-ATZ) molecule is retained in the endoplasmic reticulum of liver cells rather than secreted into the blood and body fluids. Emphysema is thought to be caused by the lack of circulating .alpha.1-AT to inhibit neutrophil elastase in the lung. Liver injury is thought to be caused by the hepatotoxic effects of the retained .alpha.1-ATZ. In this study, we show that several 'chemical chaperones,' which have been shown to reverse the cellular mislocalization or misfolding of other mutant ***plasma*** membrane, nuclear, and cytoplasmic proteins, mediate increased secretion of .alpha.1-ATZ. In particular, 4- phenylbutyric acid (PBA) mediated a marked increase in secretion of functionally active .alpha.1-ATZ in a model cell culture system. Moreover, oral ***administration*** of PBA was well tolerated by PiZ mice (transgenic for the human .alpha.1-ATZ gene) and consistently mediated an increase in blood ***levels*** of human .alpha.1-AT reaching 20-50% of the ***levels*** present in PiM mice and normal humans. Because clinical studies have suggested that only partial correction is needed for prevention of both liver and lung injury in .alpha.1-AT ***deficiency*** and PBA has been used safely in humans, it constitutes an excellent candidate for chemoprophylaxis of target organ injury in .alpha.1-AT ***deficiency*** .

L25 ANSWER 56 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1998:28491681 BIOTECHNO
TI Acute allergic reaction and demonstration of specific IgE antibodies against .alpha.-1-protease inhibitor
AU Meyer F.J.; Wencker M.; Teschler H.; Steveling H.; Sennekamp J.; Costabel

U.; Konietzko N.
CS N. Konietzko, Ruhrlandklink, Dept of Pneumology, University of Essen, Tuschenerweg 40, D-45239 Essen, Germany.
SO European Respiratory Journal, (***1998***), 12/4 (996-997), 17 reference(s)
CODEN: ERJOEI ISSN: 0903-1936
DT Journal; Article
CY Denmark
LA English
SL English
AB A 44 yr-old female with severe pulmonary emphysema and reduced .alpha.1-protease inhibitor (.alpha..sub.1-PI) ***serum*** ***levels*** developed an acute anaphylactic reaction following the third ***intravenous*** infusion of human .alpha..sub.1-PI which was ***administered*** to prevent the progression of pulmonary emphysema. Specific immunoglobulin E-antibodies against human .alpha..sub.1-PI could be demonstrated in the patient's ***serum*** using an enzyme allergosorbent test. Because of the risk of further severe anaphylactic reaction, the replacement therapy with .alpha..sub.1- PI was discontinued. Physicians should be aware of this rare complication.

L25 ANSWER 57 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1997:27187561 BIOTECHNO
TI Alpha.sub.1-antitrypsin ***deficiency*** and asthma: The continuing search for the relationship
AU Pina J.S.; Horan M.P.
CS J.S. Pina, Pulmonary and Critical Care Service, Tripler Army Medical Center, Honolulu, HI 96859, United States.
SO Postgraduate Medicine, (***1997***), 101/4 (153-156+159-162+167-168), 19 reference(s)
CODEN: POMDAS ISSN: 0032-5481
DT Journal; General Review
CY United States
LA English
SL English
AB Patients with alpha.sub.1-antitrypsin (AAT) ***deficiency*** , like those with asthma and chronic obstructive pulmonary disease, usually present with dyspnea, wheeze, and cough. The similarity in presentation and unfamiliarity among clinicians with AAT ***deficiency*** account for much of the delay in diagnosis. Normally, AAT inhibits serine proteases, which cause alveolar destruction, and alters the function of cells that release mediators of inflammation. Diagnostic findings suggesting ***deficiency*** include irreversible airflow obstruction, a decreased diffusing capacity of the lung for carbon monoxide, bibasilar bullous disease on chest films, and a low ***serum*** ***level*** of AAT. Asthma is usually diagnosed on the basis of clinical findings and response to inhaled beta agonists. The presence of inflammation is believed to be necessary for development of clinically significant asthma. Inflammation added to a ***deficiency*** of antiprotease inhibitor activity significantly worsens bronchial hyperreactivity. This is only one mechanism by which AAT ***deficiency*** may potentiate allergic and bronchospastic responses. The prevalence of bronchial asthma in patients with AAT ***deficiency*** is unknown. Studies by the National Institutes of Health regarding the natural history of AAT ***deficiency*** and its response to therapy are under way. Perhaps more will be discovered about the relationship between the disorder and bronchial asthma.

L25 ANSWER 58 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1996:26229081 BIOTECHNO
TI ***Alpha*** ***1*** ***antitrypsin*** defective Lewis rats injected with heparin: Comparison of the glomerular changes with those of

Lewis rats produced anti BSA antibody
AU Nakatsuji T.
CS Department of Transfusion, Hamamatsu Univ. School of Medicine, 3600 Handa-cho,Hamamatsu, Shizuoka 431-31, Japan.
SO Keio Journal of Medicine, (***1996***), 45/2 (109-113)
CODEN: KJMEA0 ISSN: 0022-9717
DT Journal; Article
CY Japan
LA English
SL English
AB Heparin effects were studied on Lewis rats with .alpha..sub.1 antitrypsin (AT) defect. Among 8 rats that were born at the same birth, three rats were shown to have mild defect of .alpha..sub.1 AT. Heparin was injected repeatedly into all the 8 rats. Interstitial pneumonia and localized periodic acid-Schiff (PAS) stain of hepatocytes were found in .alpha..sub.1 AT defective male. One of the three .alpha..sub.1 AT defective rats had about a half of normal .alpha..sub.1 AT ***level*** . Antithrombin (AT) III ***level*** was slightly low in the .alpha..sub.1 AT defective female with splenomegaly. Lung electron micrograph of the other .alpha..sub.1 AT defective female showed edematous changes of capillaries and alveolar basement membranes and also proliferated collagen fibers. In the lung of .alpha..sub.1 AT defective male, many thrombocytes adhered to alveolar degenerated smooth muscles that were recognized as Masson bodies. Extracted platelet-activating factor (PAF) in the ***plasma*** of the .alpha..sub.1 AT defective male was shown to trigger T lymphocyte chemotaxis. Five normal Lewis rats were immunized with bovine ***serum*** albumin (BSA). IgG1 antibody to BSA was produced in all the rats. The rats with high titers of IgG1 anti BSA antibody showed more strongly atrophic changes of glomerulus than those of the mild .alpha..sub.1 AT defective rats treated with heparin.

L25 ANSWER 59 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1990:20118572 BIOTECHNO
TI Augmentation therapy of .alpha..sub.1-antitrypsin ***deficiency***
AU Hubbard R.C.; Crystal R.G.
CS Pulmonary Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, United States.
SO European Respiratory Journal, (***1990***), 3/SUPPL. 9 (44s-52s)
CODEN: ERJOEI ISSN: 0904-1850
DT Journal; Conference Article
CY Denmark
LA English
SL French; English
AB ***Intravenous*** augmentation therapy with human ***plasma*** .alpha..sub.1AT represents the current 'state of the art' form of therapy for .alpha..sub.1AT ***deficiency*** . Augmentation therapy is directed towards specific correction of the central abnormality of .alpha..sub.1AT ***deficiency*** i.e., to correct the insufficient anti-neutrophil elastase screen of the lung. By augmenting lung ***levels*** of functional .alpha..sub.1AT, the anti-neutrophil elastase protective screen of the lower respiratory tract is re-established, and the delicate alveolar structures are protected from elastolytic degradation. Weekly, monthly and ***plasma*** exchange-.alpha..sub.1AT infusion all share the same basic approach to augmenting lung anti-elastase defenses, and appear to be equally effective in re-establishing the anti-elastase screen of the lower respiratory tract. One important issue concerning augmentation therapy is the question of when to initiate therapy. Because the goal of augmentation therapy is to prevent lung destruction, it is rational to initiate therapy prior to the onset of significant lung destruction. Traditionally, pulmonary function testing and chest X-rays have been used

to determine the degree of emphysema, but these methods are relatively insensitive when compared to newer evaluative methods, including computed tomography and ventilation-perfusion scanning. In view of the availability of these newer diagnostic modalities, and the desire to maximally preserve the lung through early initiation of augmentation therapy, the traditional concepts requiring the presence of lung function abnormalities as evidence of lung destruction may need to be re-evaluated for individuals with .alpha..sub.1AT ***deficiency*** . Aerosol augmentation therapy with human ***plasma*** .alpha..sub.1AT or with rAAT are attractive possible alternative approaches to increasing lung anti-neutrophil elastase defenses. By directing targeting active anti-elastase protection to the lung via aerosol, this form of therapy offers the prospect of significantly more efficient delivery of equivalent therapy, and the possibility of patient self-***administration*** , thus lessening the burden of the disease to patients. However, evaluation of aerosol therapy in the form of long-term study will be necessary before it is possible to recommend aerosol augmentation therapy as clinically equivalent to ***intravenous*** therapy. Gene therapy represents the likely future of augmentation therapy. As with liver transplantation, successful gene therapy would directly cure the ***deficiency*** state. Unlike liver transplantation, gene therapy would not be limited by the major practical constraints imposed by the limited availability of donor organs. Although considerable methodological hurdles remain prior to gene therapy becoming an established therapeutic modality for .alpha..sub.1AT ***deficiency*** , it holds forth the promise of curative therapy, and will continue to be the subject of active investigation.

L25 ANSWER 60 OF 60 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 1980:10071351 BIOTECHNO
TI Danazol-induced augmentation of ***serum*** . ***alpha*** . ***1*** - ***antitrypsin*** ***levels*** in individuals with marked ***deficiency*** of this antiprotease
AU Gadek J.E.; Fulmer J.D.; Gelfand J.A.; et al.
CS Pulmon. Branch, Nat. Heart Lung Blood Inst., Bethesda, Md. 20205, United States.
SO Journal of Clinical Investigation, (***1980***), 66/1 (82-87)
CODEN: JCINAO
DT Journal; Article
CY United States
LA English
AB Individuals with ***serum*** . ***alpha*** . ***1*** - ***antitrypsin*** ***levels*** below 80 mg/dl are clearly at risk for the development of accelerated panacinar emphysema. One possible approach to the therapy of this disorder would be to raise ***serum*** ***levels*** of this major antiprotease to establish protease-antiprotease homeostasis within the lung parenchyma. Because danazol, an impeded androgen, elevates ***levels*** of C1 inhibitor in patients ***deficient*** of that ***serum*** antiprotease, the authors hypothesized that this agent might also increase . ***alpha*** . ***1*** - ***antitrypsin*** ***levels*** in patients with . ***alpha*** . ***1*** - ***antitrypsin*** ***deficiency*** . To evaluate this concept, seven patients with severe emphysema associated with . ***alpha*** . ***1*** - ***antitrypsin*** ***deficiency*** .cents.six PiZ and 1 M(Duarte)Z! and one asymptomatic individual (PiSZ) received 600 mg of danazol daily for 30 days. Five of the six PiZ patients responded to danazol therapy with significant increases in ***serum*** . ***alpha*** . ***1*** - ***antitrypsin*** ***levels*** (mean increase of 37%; P < 0.03). The two individuals who were heterozygous for the Z protein increased their ***serum*** ***levels*** by 85% .cents.PiM(Duarte)Z! and 87% (PiSZ), respectively. These increases in ***serum*** .

alpha . ***1*** - ***antitrypsin*** antigen were accompanied by commensurate increases in ***serum*** trypsin inhibition. Crossed immunoelectrophoresis showed no alterations of the microheterogeneity of the . ***alpha*** . ***1*** - ***antitrypsin*** or the presence of protease-antiprotease complexes in ***serum*** during danazol therapy. These data demonstrate that ***serum*** . ***alpha*** . ***1*** - ***antitrypsin*** ***levels*** can be augmented by danazol therapy in PiZ individuals as well as those heterozygotes with severe ***deficiency*** of . ***alpha*** . ***1*** - ***antitrypsin*** . The clinical relevance of these increases in ***serum*** . ***alpha*** . ***1*** - ***antitrypsin*** remains speculative, but these findings suggest that danazol may provide a means of improving the protease-antiprotease balance in these individuals and thus impede the progression of their lung disease.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	239.42	336.94

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.50	-1.50

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